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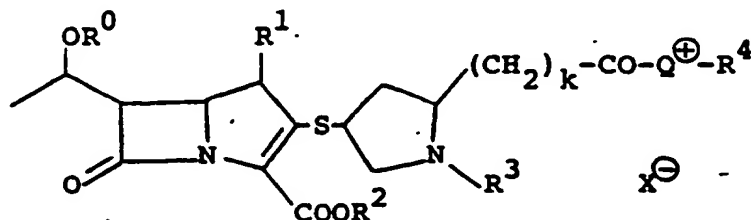
Applicant: **SUMITOMO PHARMACEUTICALS  
COMPANY, LIMITED**  
**2-8, Doshomachi 2-chome, Chuo-ku**  
**Osaka-shi Osaka 541(JP)**

Inventor: **Sunagawa, Makoto**  
**29-1, Azanobata, Yamada**  
**Itami, Hyogo(JP)**  
Inventor: **Sasaki, Akira**  
**4-2-301, Ryodo-cho**  
**Nishinomiya, Hyogo(JP)**  
Inventor: **Yamaga, Hiroshi**  
**2-1-117, Kuwata-cho**  
**Ibaraki, Osaka(JP)**  
Inventor: **Fukasawa, Masatomo**  
**4-27-10, Gotenyama**  
**Takarazuka, Hyogo(JP)**  
Inventor: **Nouda, Hiroshi**  
**2-29-7, Oike**  
**Ibaraki, Osaka(JP)**

Representative: **Vossius & Partner**  
**Siebertstrasse 4 P.O. Box 86 07 67**  
**W-8000 München 86(DE)**

**Novel beta-lactam compounds and their production.**

A compound of the formula:



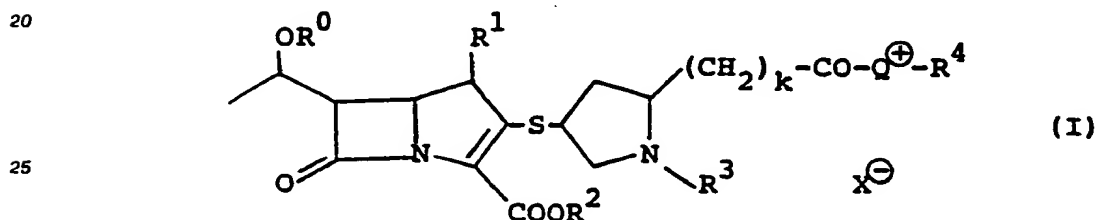
, which is useful as an antimicrobial agent.

The present invention relates to  $\beta$ -lactam compounds and their production. More particularly, it relates to novel 3-pyrrolidinylthio-1-azabicyclo[3.2.0]hept-2-en-7-one-2-carboxylic acid compounds bearing a quaternary ammonium group on the pyrrolidine ring and their production.

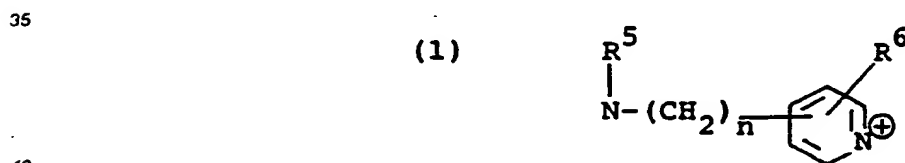
There are known some  $\beta$ -lactam compounds having a carbapenem skeleton, which possess an excellent antimicrobial spectrum against a wide range of Gram-positive and Gram-negative bacteria. Among them, imipenem is already available on the market. Since, however, imipenem is sensitive to renal dehydropeptidase-I (DHP-I) in a living body and apt to be inactivated, it is normally used in combination with cylastatin for preventing the inactivation with DHP-I. Needless to say, it is clinically favorable that an antimicrobial agent exerts its antimicrobial activity without any auxiliary agent, and a great demand is present towards the development of a  $\beta$ -lactam compound which exerts its antimicrobial activity with resistance to DHP-I, i.e. saving the use of any auxiliary agent.

As the result of an extensive study, it has now been found that some 3-pyrrolidinylthio-1-azabicyclo[3.2.0]hept-2-en-7-one-2-carboxylic acid compounds having a quaternary ammonium group on the pyrrolidine ring exerts a strong antimicrobial activity with sufficient resistance to DHP-I. The present invention is based on the above finding.

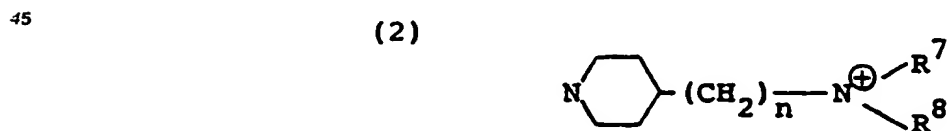
Accordingly, a basic object of the present invention is to provide a novel  $\beta$ -lactam compound of the formula:



wherein  $R^0$  is a hydrogen atom or a protective group for hydroxyl,  $R^1$  is a lower alkyl group,  $R^2$  is a protective group for carboxyl or a negative charge,  $R^3$  is a hydrogen atom or a protective group for amino,  $R^4$  is a lower alkyl group or a substituted lower alkyl group,  $k$  is an integer of 0 to 4,  $X$  is an acid residue or intramolecular COO when  $R^2$  is the negative charge and  $Q^+$  is a quaternary nitrogen atom-containing group represented by either one of the formulas (1) to (4):



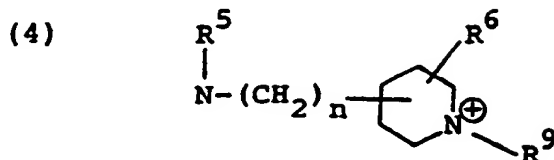
wherein  $R^5$  is a hydrogen atom, a lower alkyl group or a 2-hydroxyethyl group,  $R^6$  is a hydrogen atom or a lower alkyl group and  $n$  is an integer of 0 to 4;



wherein  $R^7$  and  $R^8$  are each a lower alkyl group or may be combined together to form a lower alkylene group, or  $R^8$  represents a substituted lower alkyl group and  $n$  is as defined above;

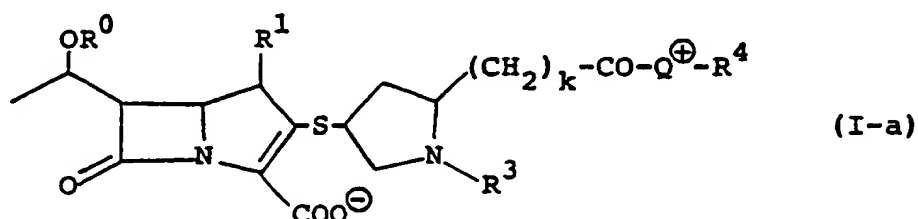


wherein  $R^3$  is a lower alkyl group or a substituted lower alkyl group; or



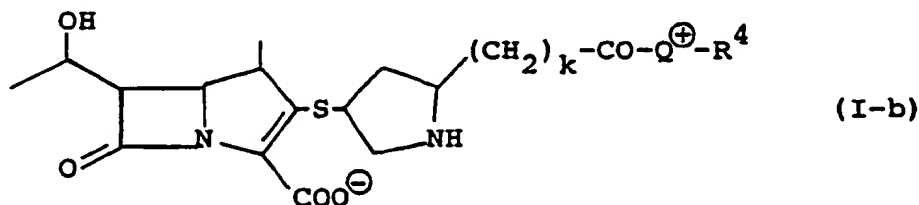
wherein  $R^5$ ,  $R^6$ ,  $R^9$  and  $n$  are each as defined above.

When  $R^2$  is a negative charge and  $X$  is intra-molecular COO, the  $\beta$ -lactam compound (I) forms an intra-molecular quaternary salt, which is represented by the formula:



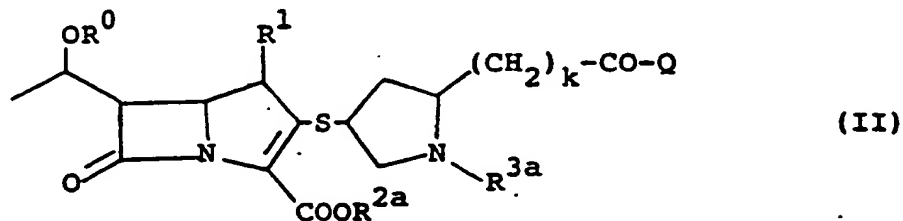
wherein  $R^0$ ,  $R^1$ ,  $R^3$ ,  $R^4$ ,  $k$  and  $Q^+$  are each as defined above.

Among various  $\beta$ -lactam compounds which fall within the formula (I), the most preferred are those of the formula:



wherein  $R^4$ ,  $k$  and  $Q^+$  are each as defined above.

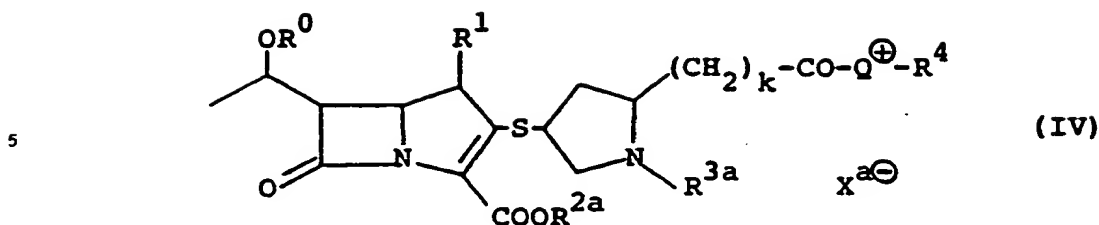
According to the present invention, the  $\beta$ -lactam compound (I) can be produced by reacting a  $\beta$ -lactam compound of the formula:



wherein  $R^0$ ,  $R^1$  and  $k$  are each as defined above,  $R^{2a}$  is a protective group for carboxyl,  $R^{3a}$  is a protective group for amino and  $Q$  is a tertiary nitrogen atom-containing group resulting from elimination of a positive charge from either one of the groups (1) to (4) represented by  $Q^+$  with a compound of the formula:



wherein  $R^4$  is as defined above and  $X^a$  is an acid residue to give a  $\beta$ -lactam compound of the formula:



10 wherein  $R^0$ ,  $R^1$ ,  $R^{2a}$ ,  $R^{3a}$ ,  $R^4$ ,  $k$ ,  $Q^+$  and  $X^a$  are each as defined above, optionally followed by subjecting the  $\beta$ -lactam compound (IV) to elimination of the hydroxyl-protecting group represented by  $R^0$ , elimination of the carboxyl-protecting group represented by  $R^{2a}$  and/or elimination of the amino-protecting group represented by  $R^{3a}$ , thereby giving the  $\beta$ -lactam compound (I) wherein  $R^0$  and  $R^3$  are each a hydrogen atom and  $R^2$  is a negative charge.

15 With respect to the definitions of the symbols as given above, the term "lower" is intended to mean a group normally having not more than 8 carbon atoms, preferably not more than 5 carbon atoms.

The protective group for hydroxyl (i.e. hydroxyl-protecting group) represented by  $R^0$  and the protective group for amino (i.e. amino-protecting group) represented by  $R^3$  or  $R^{3a}$  may be any group as conventionally used in the related art field. Preferred examples are  $C_1$ - $C_5$  alkoxycarbonyl (e.g. t-butyloxycarbonyl), halo-  
 20 ( $C_1$ - $C_5$ )alkoxycarbonyl (e.g. 2-iodoethyloxycarbonyl, 2,2,2-trichloroethyloxycarbonyl),  $C_3$ - $C_7$  alkenyloxycarbonyl (e.g. allyloxycarbonyl), ar( $C_1$ - $C_3$ )alkyloxycarbonyl such as phenyl( $C_1$ - $C_3$ )alkyloxycarbonyl (e.g. benzyloxycarbonyl) or substituted phenyl( $C_1$ - $C_3$ )alkyloxycarbonyl (e.g. p-methoxybenzyloxycarbonyl, o-nitrobenzyloxycarbonyl, p-nitrobenzyloxycarbonyl), and tri( $C_1$ - $C_5$ )alkylsilyl (e.g. trimethylsilyl, t-butyl-dimethylsilyl) groups.

25 The protective group for carboxyl (i.e. carboxyl-protective group) represented by  $R^2$  or  $R^{2a}$  may be also any group as conventionally used. Preferred examples are straight or branched  $C_1$ - $C_5$  lower alkyl (e.g. methyl, ethyl, isopropyl, t-butyl), halo( $C_1$ - $C_5$ )alkyl (e.g. 2-iodoethyl, 2,2,2-trichloroethyl),  $C_1$ - $C_5$  alkoxymethyl (e.g. methoxyethyl, ethoxymethyl, isobutoxymethyl),  $C_1$ - $C_5$  aliphatic acyloxymethyl (e.g. acetoxymethyl, propionyloxymethyl, butyryloxymethyl, pivaloyloxymethyl), 1-( $C_1$ - $C_5$ )alkoxycarbonyloxyethyl (e.g. 1-ethoxycarbonyloxyethyl), ar( $C_1$ - $C_3$ )alkyl such as phenyl( $C_1$ - $C_3$ )alkyl (e.g. benzyl) or substituted phenyl( $C_1$ - $C_3$ )alkyl (e.g. p-methoxybenzyl, o-nitrobenzyl, p-nitrobenzyl),  $C_3$ - $C_7$  alkenyl (e.g. allyl, 2-methylallyl, 3-methylallyl), benzhydryl and phthalidyl groups.

Examples of the lower alkyl group represented by  $R^1$ ,  $R^4$ ,  $R^5$ ,  $R^6$ ,  $R^7$ ,  $R^8$  or  $R^9$  are  $C_1$ - $C_5$  alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, n-pentyl) groups. In case of the substituted lower alkyl group  
 35 represented by  $R^4$ ,  $R^8$  or  $R^9$ , the substituent on the lower alkyl group may be, for instance, carboxyl, lower alkanoyl (e.g. acetyl, propionyl), carbamoyl, lower alkylaminocarbonyl (e.g. methylaminocarbonyl), di(lower)-alkylaminocarbonyl (e.g. dimethylaminocarbonyl), cyano, lower alkoxy (e.g. methoxy, ethoxy), hydroxyl, and phenyl groups. Thus, examples of the substituted lower alkyl group are  $C_1$ - $C_7$  alkyl substituted with one or more substituents as exemplified above, specifically carboxymethyl, acetylmethyl, propionylmethyl, carbamoylmethyl, N-methylaminocarbonylmethyl, N,N-dimethylaminocarbonylmethyl, 2-cyanoethyl, 2-methoxyethyl, 2-ethoxyethyl, 2-carboxyethyl, 2-hydroxyethyl, 2-carbamoyl, 2-N-methylaminocarbonyl, 2-N,N-dimethylaminocarbonyl, 3-carboxypropyl, 4-hydroxybutyl, 5-hydroxypentyl and benzyl groups.

When  $R^7$  and  $R^8$  are combined together to make a lower alkylene group, they form a 3- to 7-membered ring together with the nitrogen atom to which they are attached, and examples of the 3- to 7-membered ring  
 45 are aziridine, azetidine, pyrrolidine and piperidine groups.

Examples of the acid residue represented by  $X$  or  $X^a$  are an inorganic acid residue (e.g. chlorine, bromine, fluorine, iodine) or an organic acid residue (e.g. benzenesulfonyloxy, p-toluenesulfonyloxy, methanesulfonyloxy, trifluoromethanesulfonyloxy).

The  $\beta$ -lactam compound (I) may be either in a free form or in a salt (preferably non-toxic salt) form.  
 50 Examples of the salt are inorganic base salts (e.g. sodium, potassium, calcium, magnesium, ammonium), organic base salts (e.g. triethylammonium, pyridinium, diisopropylammonium), inorganic acid addition salts (e.g. hydrochloride, sulfate, phosphate), and organic acid addition salts (e.g. formate, acetate, methanesulfonate, benzenesulfonate).

Production of the  $\beta$ -lactam compound (I) will be hereinafter explained in details.

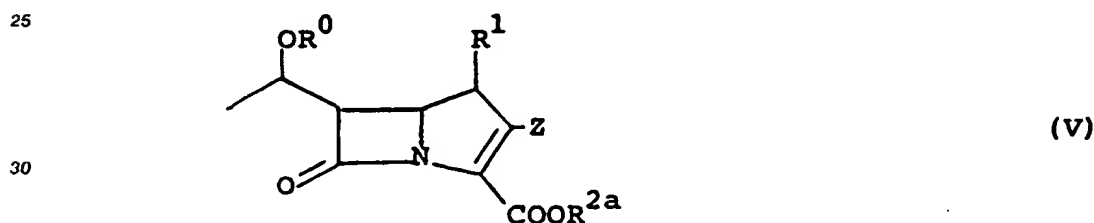
55 The quaternarization of the  $\beta$ -lactam compound (II) may be performed by a per se conventional procedure, for instance, by reacting the  $\beta$ -lactam compound (II) with the compound (III) in an inert solvent chosen from water, ketones (e.g. acetone, methyl ethyl ketone), ethers (e.g. tetrahydrofuran, dioxane), acetonitrile and halogenated hydrocarbons (e.g. dichloromethane, dichloroethane, chloroform), or their

mixtures. There is no limitation on the reaction temperature, but the reaction is normally effected at a temperature of  $-40$  to  $60^{\circ}\text{C}$ . Upon termination of the reaction, the objective product is isolated from the reaction mixture by a per se conventional procedure.

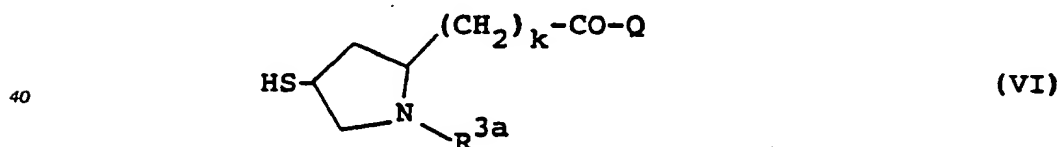
The thus obtained product, i.e. the  $\beta$ -lactam compound (IV), is optionally subjected to elimination of the hydroxyl-protecting group represented by  $\text{R}^0$ , elimination of the carboxyl-protecting group represented by  $\text{R}^{2a}$  and/or elimination of the amino-protecting group represented by  $\text{R}^{3a}$  to give the  $\beta$ -lactam compound (I) wherein at least one of  $\text{R}^0$  and  $\text{R}^3$  is a hydrogen atom and  $\text{R}^2$  is a negative charge.

The elimination may be effected independently or concurrently by a per se conventional procedure such as treatment with an acid, a base or a reducing agent (T.W.Greene: Protective Groups in Organic Synthesis, J. Wiley & Sons Inc., 1981). As the acid, there are exemplified trifluoroacetic acid, formic acid, boron trifluoride and aluminium chloride. As the base, there are exemplified alkali metal carbonate (e.g. sodium carbonate, potassium carbonate), alkali metal sulfate (e.g. sodium sulfate, potassium sulfate) and tetrafluorobutylammonium. When the elimination is conducted through reduction, there may be adopted any procedure using zinc and acetic acid, hydrogen and palladium-carbon or platinum. The elimination with tetrakis(triphenylphosphine) palladium is also available. Any particular limitation is not present on the solvent to be used, and it may be chosen from water, alcohols (e.g. methanol, ethanol), ethers (e.g. tetrahydrofuran, dioxane) and aliphatic acids (e.g. acetic acid). The reaction temperature may be appropriately decided so as to control or accelerate the proceeding of the reaction, and a preferred temperature is normally from  $-30$  to  $40^{\circ}\text{C}$ . The reaction product may be separated from the reaction mixture by a per se conventional procedure. For instance, the reaction mixture is neutralized and chromatographed on an adsorptive resin, followed by elution and lyophilization.

The  $\beta$ -lactam compound (II) as the starting compound is obtainable by reacting a  $\beta$ -lactam compound of the formula:



wherein  $\text{R}^0$ ,  $\text{R}^1$  and  $\text{R}^{2a}$  are each as defined above and Z is a reactive ester on hydroxyl with a mercaptan compound of the formula:



wherein  $\text{R}^{3a}$ , k and Q are each as defined above in an inert solvent in the presence of a base.

45 The  $\beta$ -lactam compound (V) is known (cf. Heterocycles, Vol. 21, p. 29-40, 1984), and its reactive ester on hydroxyl represented by Z may be chosen, for instance, from arylsulfonates such as benzenesulfonates and substituted benzenesulfonates (e.g. p-toluenesulfonate, p-nitrobenzenesulfonate, p-bromobenzenesulfonate),  $\text{C}_1$ - $\text{C}_5$  alkanesulfonates (e.g. methanesulfonate, ethanesulfonate), halo( $\text{C}_1$ - $\text{C}_5$ )alkanesulfonates (e.g. trifluoromethanesulfonate), diarylphosphates (e.g. diphenylphosphate) and halides (e.g. chloride, bromide, iodide). Of these, p-toluenesulfonate, methanesulfonate and diphenylphosphate are preferred.

The mercaptan compound (VI), which may be produced from trans-4-hydroxy-L-proline or cis-4-hydroxy-D-proline by a known method (cf. U.S. Patent Nos. 4,943,569 and 4,962,103), is usually employed in an excessive amount, particularly in a 1 to 2 equivalent amount to the  $\beta$ -lactam compound (V) so that the reaction with the  $\beta$ -lactam compound (V) proceeds sufficiently.

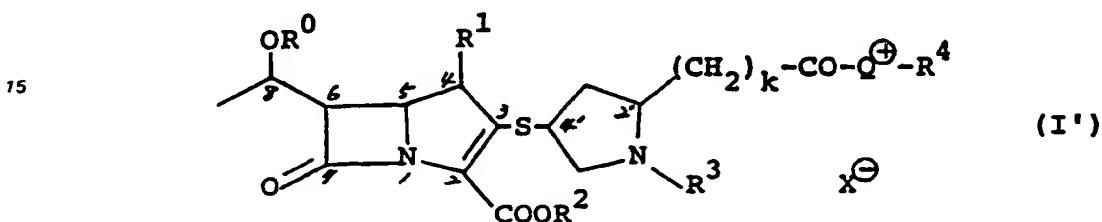
55 Examples of the inert solvent are dioxane, tetrahydrofuran, dimethylsulfoxide, acetonitrile and hexamethylphosphoramide. As the base, there may be used an inorganic base (e.g. sodium carbonate, potassium carbonate, sodium hydride, potassium hydride, potassium t-butoxide), an organic base (e.g. pyridine, dimethylaminopyridine, triethylamine, diisopropylethylamine and 1,8-diazabicyclo[5.4.0]-undec-7-

ene (DBU), among which preferred are diisopropylethylamine and DBU. The base is used in such an amount as can assure the smooth proceeding of the reaction, normally in a 1 to 3 equimolar amount to the mercaptan compound (VI).

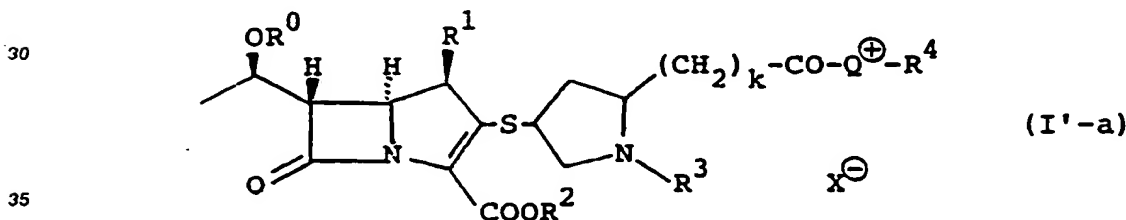
The reaction is normally carried out at a temperature of from -78 to 60° C, preferably from -40 to 40° C.

5 Upon termination of the reaction, the reaction mixture may be subjected to post-treatment in a per se conventional procedure so as to obtain the objective  $\beta$ -lactam compound (II), if necessary, followed by purification.

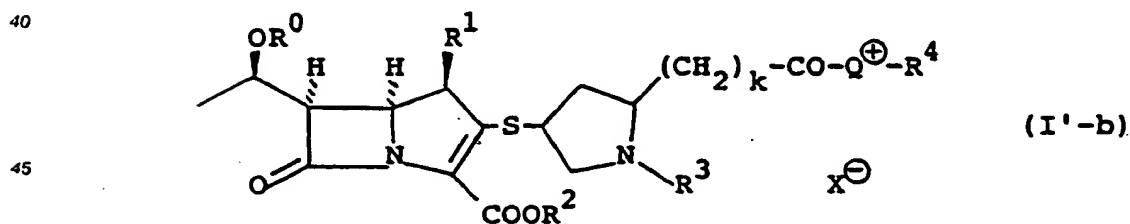
The  $\beta$ -lactam compound (I) of the invention includes asymmetric carbon atoms at the 4-, 5-, 6- and 8-positions in the carbapenem skeleton as shown in the following formula and has optical and steric isomers  
10 due to those asymmetric carbon atoms:



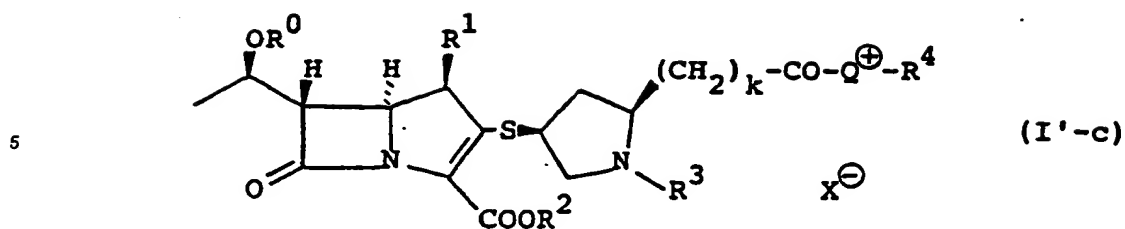
wherein  $R^0$ ,  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$ ,  $k$  and  $Q^+$  and  $X^-$  are each as defined above. While all these optical and steric isomers and their mixtures fall within the scope of the invention, preferred are those having an S-configuration at the 5-position, i.e. (5S,6S) or (5S,6R), those having an R-configuration at the 8-position and  
25 those having an R configuration at the 4-position. More preferred are those having a (4R,5S,6S,8R) configuration as represented by the formula (I'-a) or a (4R,5S,6R,8R) configuration as represented by the formula (I'-b):



and



wherein  $R^0$ ,  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$ ,  $k$ ,  $Q^+$  and  $X^-$  are each as defined above. The most preferred are those of the  
50 formula (I'-c):



10 wherein  $R^0$ ,  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$ ,  $k$ ,  $Q^+$  and  $X^{\ominus}$  are each as defined above.

Production of the specific isomers as above stated can be achieved by the use of the corresponding isomers of the  $\beta$ -lactam compound (V) and the mercaptan compound (VI).

15 Typical examples of the  $\beta$ -lactam compound (I) wherein  $R^0$  and  $R^3$  are each a hydrogen atom,  $R^1$  is a methyl group and  $R^2$  is a negative charge are shown in Table 1, in which Me and Ph indicate respectively methyl and phenyl.

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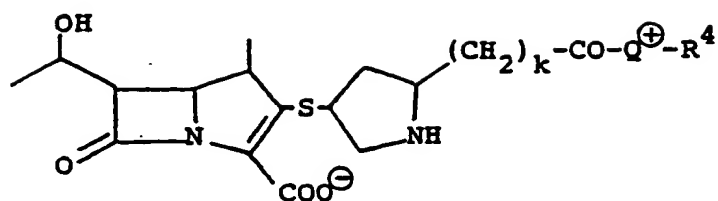
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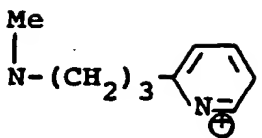
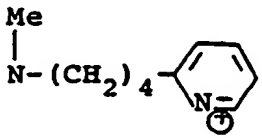
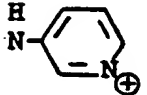
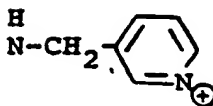
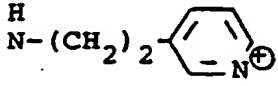
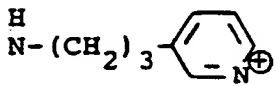
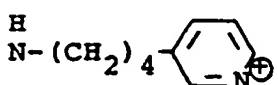
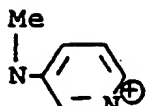
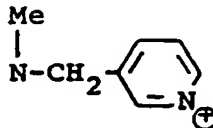
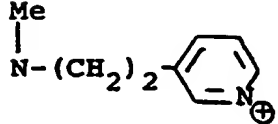
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Table 1

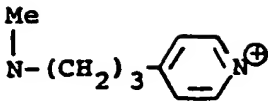
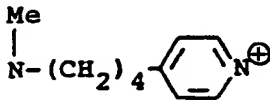
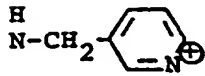
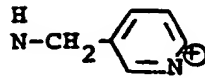
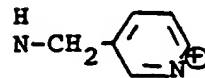
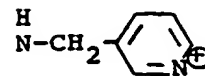
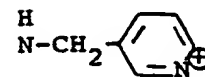
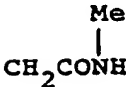
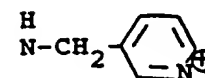
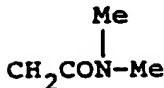
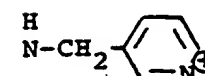
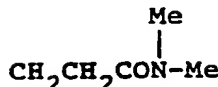
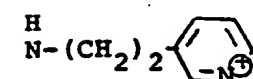
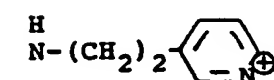
<u>Compound No.</u>	<u>k</u>	<u>Q<sup>+</sup></u>	<u>R<sup>4</sup></u>
1	0		Me
2	0		Me
3	0		Me
4	0		Me
5	0		Me
6	0		Me
7	0		Me
8	0		Me

	<u>Compound No.</u>	<u>k</u>	<u><math>\Omega^{\oplus}</math></u>	<u>R<sup>4</sup></u>
5	9	0		Me
10	10	0		Me
15	11	0		Me
20	12	0		Me
25	13	0		Me
30	14	0		Me
35	15	0		Me
40	16	0		Me
45	17	0		Me
50	18	0		Me

55

	Compound No.	$k$	$Q^{\oplus}$	$R^4$
5	19	0		Me
10	20	0		Me
15	21	0		Me
20	22	0		Me
25	23	0		Me
30	24	0		Me
35	25	0		Me
40	26	0		Me
45	27	0		Me
50	28	0		Me




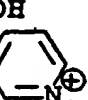
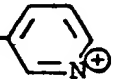

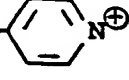
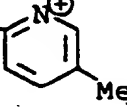
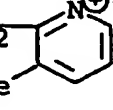
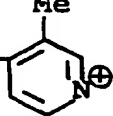
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	<u>Compound No.</u>	<u>k</u>	<u>Q<sup>+</sup></u>	<u>R<sup>4</sup></u>
5	29	0		Me
10	30	0		Me
15	31	0		CH <sub>2</sub> Ph
20	32	0		CH <sub>2</sub> COOH
25	33	0		CH <sub>2</sub> CH <sub>2</sub> OH
30	34	0		CH <sub>2</sub> CONH <sub>2</sub>
35	35	0		
40	36	0		
45	37	0		
50	38	0		CH <sub>2</sub> Ph
55	39	0		CH <sub>2</sub> COOH

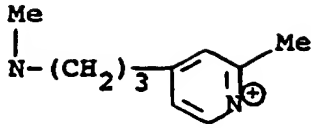



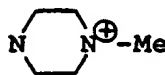
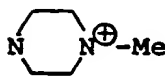
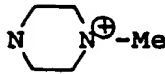
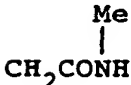

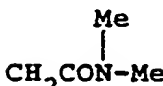

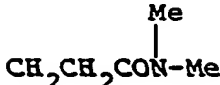




	<u>Compound N .</u>	<u>k</u>	<u>Q<sup>+</sup></u>	<u>R<sup>4</sup></u>
5	40	0	$\text{H}-\text{N}-(\text{CH}_2)_2-\text{C}_5\text{H}_4\text{N}^+$	$\text{CH}_2\text{CH}_2\text{OH}$
10	41	0	$\text{H}-\text{N}-(\text{CH}_2)_2-\text{C}_5\text{H}_4\text{N}^+$	$\text{CH}_2\text{CONH}_2$
15	42	0	$\text{H}-\text{N}-(\text{CH}_2)_2-\text{C}_5\text{H}_4\text{N}^+$	$\text{CH}_2\text{CONHMe}$
20	43	0	$\text{H}-\text{N}-(\text{CH}_2)_2-\text{C}_5\text{H}_4\text{N}^+$	$\text{CH}_2\text{CONMe}_2$
25	44	0	$\text{H}-\text{N}-(\text{CH}_2)_2-\text{C}_5\text{H}_4\text{N}^+$	$\text{CH}_2\text{CH}_2\text{CONMe}_2$
30	45	0	$\text{Me}-\text{N}-(\text{CH}_2)_2-\text{C}_5\text{H}_4\text{N}^+$	$\text{PhCH}_2$
35	46	0	$\text{Me}-\text{N}-(\text{CH}_2)_2-\text{C}_5\text{H}_4\text{N}^+$	$\text{CH}_2\text{COOH}$
40	47	0	$\text{Me}-\text{N}-(\text{CH}_2)_2-\text{C}_5\text{H}_4\text{N}^+$	$\text{CH}_2\text{CH}_2\text{OH}$
45	48	0	$\text{Me}-\text{N}-(\text{CH}_2)_2-\text{C}_5\text{H}_4\text{N}^+$	$\text{CH}_2\text{CONH}_2$
50	49	0	$\text{Me}-\text{N}-(\text{CH}_2)_2-\text{C}_5\text{H}_4\text{N}^+$	$\text{CH}_2\text{CONHMe}$
55	50	0	$\text{Me}-\text{N}-(\text{CH}_2)_2-\text{C}_5\text{H}_4\text{N}^+$	$\text{CH}_2\text{CONMe}_2$

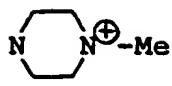

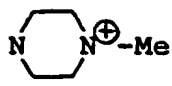

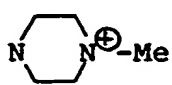

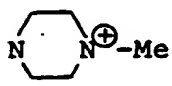
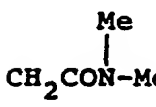
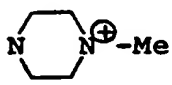
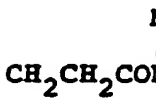
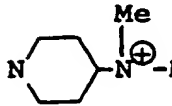
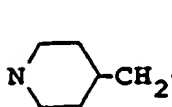
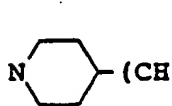
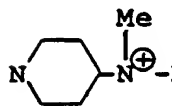
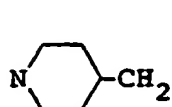
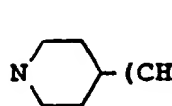
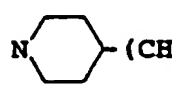
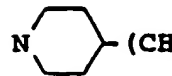
	<u>Compound No.</u>	<u>k</u>	<u>Q<sup>+</sup></u>	<u>R<sup>4</sup></u>
5	51	0		
10	52	0		CH <sub>2</sub> Ph
15	53	0		CH <sub>2</sub> COOH
20	54	0		CH <sub>2</sub> CH <sub>2</sub> OH
25	55	0		CH <sub>2</sub> CONH <sub>2</sub>
30	56	0		
35	57	0		
40	58	0		
45	59	0		CH <sub>2</sub> Ph
50	60	0		CH <sub>2</sub> COOH
55				

Compound No.	<u>k</u>	<u>Q<sup>+</sup></u>	<u>R<sup>4</sup></u>
61	0	$\begin{array}{c} \text{M} \\   \\ \text{N}-(\text{CH}_2)_3-\text{C}_6\text{H}_4-\text{N}^{\oplus} \end{array}$	$\text{CH}_2\text{CH}_2\text{OH}$
62	0	$\begin{array}{c} \text{Me} \\   \\ \text{N}-(\text{CH}_2)_3-\text{C}_6\text{H}_4-\text{N}^{\oplus} \end{array}$	$\text{CH}_2\text{CONH}_2$
63	0	$\begin{array}{c} \text{Me} \\   \\ \text{N}-(\text{CH}_2)_3-\text{C}_6\text{H}_4-\text{N}^{\oplus} \end{array}$	$\begin{array}{c} \text{Me} \\   \\ \text{CH}_2\text{CONH} \end{array}$
64	0	$\begin{array}{c} \text{Me} \\   \\ \text{N}-(\text{CH}_2)_3-\text{C}_6\text{H}_4-\text{N}^{\oplus} \end{array}$	$\begin{array}{c} \text{Me} \\   \\ \text{CH}_2\text{CON}-\text{Me} \end{array}$
65	0	$\begin{array}{c} \text{Me} \\   \\ \text{N}-(\text{CH}_2)_3-\text{C}_6\text{H}_4-\text{N}^{\oplus} \end{array}$	$\begin{array}{c} \text{Me} \\   \\ \text{CH}_2\text{CH}_2\text{CON}-\text{Me} \end{array}$
66	1	$\begin{array}{c} \text{H} \\   \\ \text{N}-\text{CH}_2-\text{C}_6\text{H}_4-\text{N}^{\oplus} \end{array}$	Me
67	1	$\begin{array}{c} \text{H} \\   \\ \text{N}-(\text{CH}_2)_2-\text{C}_6\text{H}_4-\text{N}^{\oplus} \end{array}$	Me
68	1	$\begin{array}{c} \text{H} \\   \\ \text{N}-(\text{CH}_2)_3-\text{C}_6\text{H}_4-\text{N}^{\oplus} \end{array}$	Me
69	1	$\begin{array}{c} \text{Me} \\   \\ \text{N}-(\text{CH}_2)_3-\text{C}_6\text{H}_4-\text{N}^{\oplus} \end{array}$	Me
70	2	$\begin{array}{c} \text{H} \\   \\ \text{N}-\text{CH}_2-\text{C}_6\text{H}_4-\text{N}^{\oplus} \end{array}$	Me



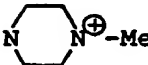
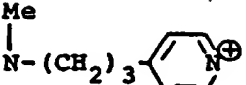
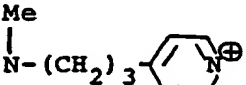
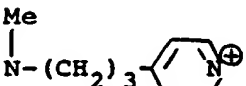
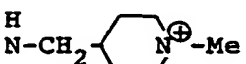
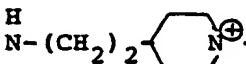
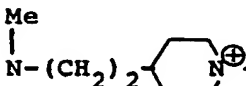
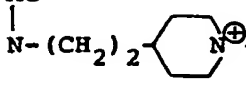
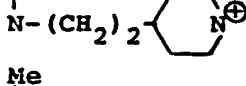
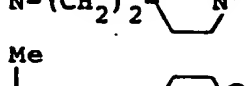
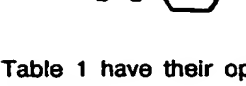
Compound No.	$k$	$\underline{Q^+}$	$\underline{R^4}$
71	2	$\text{H}$ $\text{N}-(\text{CH}_2)_2$ - 	Me
72	2	$\text{H}$ $\text{N}-(\text{CH}_2)_3$ - 	Me
73	2	$\text{Me}$ $\text{N}-(\text{CH}_2)_3$ - 	Me
74	0	$\text{CH}_2\text{CH}_2\text{OH}$ $\text{N}-\text{CH}_2$ - 	Me
75	0	$\text{CH}_2\text{CH}_2\text{OH}$ $\text{N}-(\text{CH}_2)_2$ - 	Me
76	0	$\text{CH}_2\text{CH}_2\text{OH}$ $\text{N}-(\text{CH}_2)_2$ - 	Me
77	0	$\text{CH}_2\text{CH}_2\text{OH}$ $\text{N}-(\text{CH}_2)_3$ - 	Me
78	0	$\text{H}$ $\text{N}-(\text{CH}_2)_2$ - 	Me
79	0	$\text{H}$ $\text{N}-(\text{CH}_2)_2$ - 	Me
80	0	$\text{Me}$ $\text{N}-(\text{CH}_2)_3$ - 	Me



Compound No.	<u>k</u>	<u>Q<sup>+</sup></u>	<u>R<sup>4</sup></u>
81	0		Me
82	0		Me
83	0		CH <sub>2</sub> Ph
84	0		CH <sub>2</sub> COOH
85	0		CH <sub>2</sub> CH <sub>2</sub> OH
86	0		CH <sub>2</sub> CONH <sub>2</sub>
87	0		
88	0		
89	0		
90	1		Me
91	1		CH <sub>2</sub> Ph
92	1		CH <sub>2</sub> COOH
93	1		CH <sub>2</sub> CH <sub>2</sub> OH

	<u>Compound No.</u>	<u>k</u>	<u>Q<sup>+</sup></u> 	<u>R<sup>4</sup></u> 
5	94	1		
	95	1		
10	96	1		
15	97	1		
20	98	0		Me
	99	0		Me
25	100	0		Me
30	101	1		Me
35	102	1		Me
40	103	1		Me
45	104	0		Me
50	105	0		Me

55

	Compound No.	k	$\text{O}^{\oplus}$	$\text{R}^4$
5	106	0		$\text{CH}_2\text{CH}_2\text{CN}$
	107	0		$\text{CH}_2\text{CH}_2\text{OMe}$
10	108	0		$\text{CH}_2\text{CO-Me}$
15	109	0		$\text{CH}_2\text{CH}_2\text{CN}$
20	110	0		$\text{CH}_2\text{CH}_2\text{OMe}$
25	111	0		$\text{CH}_2\text{CO-Me}$
30	112	0		Me
	113	0		Me
35	114	0		Me
40	115	0		$\text{CH}_2\text{COOH}$
	116	0		$\text{CH}_2\text{CH}_2\text{OH}$
45	117	0		$\text{CH}_2\text{CONH}_2$
50	118	1		$\text{CH}_2\text{CO-Me}$

55 The  $\beta$ -lactam compounds as exemplified in Table 1 have their optical and steric isomers, and all of them are included within the scope of the present invention.

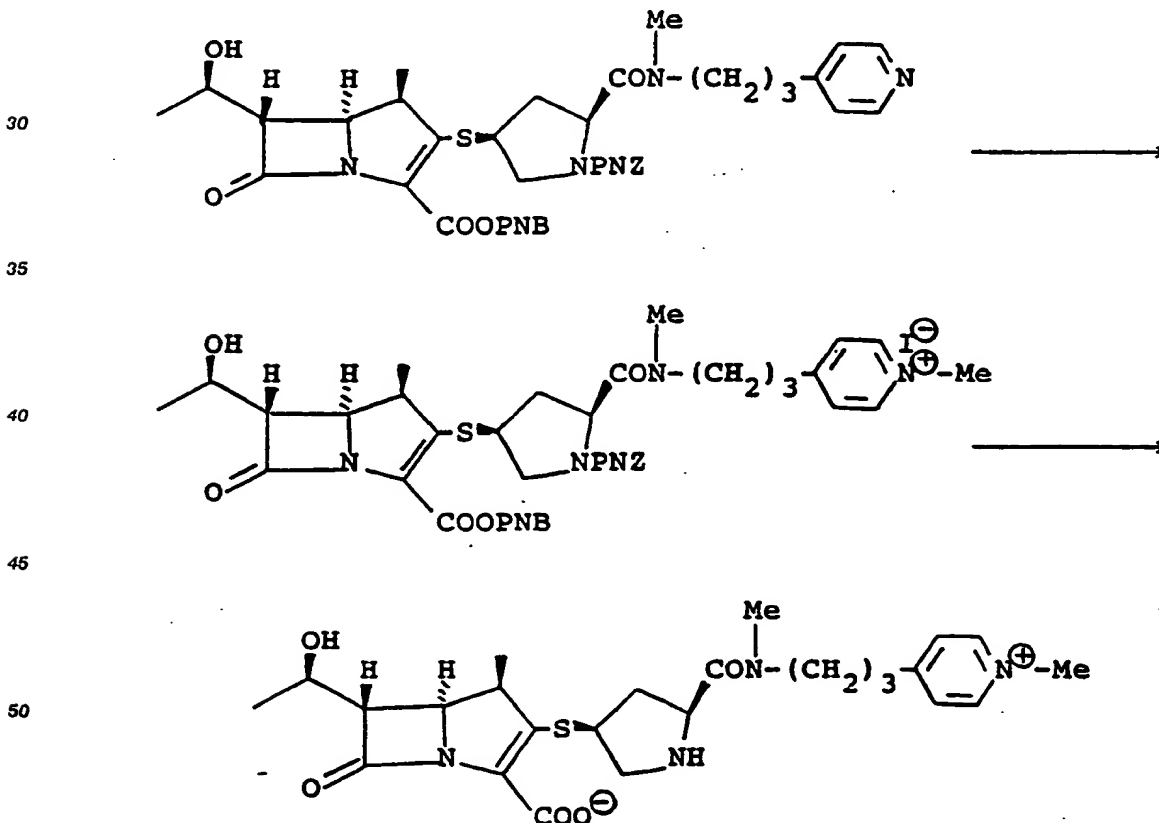
The  $\beta$ -lactam compounds (I) according to the invention are characteristic in having a 2-substituted pyrrolidin-4-ylthio group introduced with a quaternary ammonium group at the 3-position and a low  $r$  alkyl group at the 4-position in the carbapenem skeleton. Due to such characteristic structure, the  $\beta$ -lactam

compounds (I) exert an excellent antimicrobial activity against Gram-positive and Gram-negative bacteria including *Staphylococcus aureus*, *Streptococcus pyogenes*, *Escherichia coli*, *Serratia marcescens* and *Pseudomonas aeruginosa*. It is notable that while conventional carbapenem compounds such as imipenem are generally unstable in a living body, especially sensitive to renal DHP-I, the  $\beta$ -lactam compounds (I), particularly those wherein R<sup>1</sup> is a methyl group in the R-configuration, are in general significantly resistant to renal DHP-I. It is also notable that the half life time (T<sub>1/2</sub>) of the  $\beta$ -lactam compounds (I) in a living body is generally longer than that of conventional carbapenem compounds such as imipenem. The  $\beta$ -lactam compounds (I) are thus useful as antimicrobial drugs or intermediates in the synthesis of such antimicrobial drugs.

For the practical usage of the  $\beta$ -lactam compounds (I) as antimicrobial drugs, they may be formulated into conventional preparation forms together with excipients or additives such as carriers, diluents, binders and stabilizers and administered in various modes, of which examples are oral administration in the form of tablets, capsules, dispersants and syrups, non-oral administration in the form of injection through vein, muscle or rectum. When they are applied in injection forms, the preparations may additionally include buffering agents, solubilizing agents and isotonic agents. The daily dosage may vary depending upon the state of disease, the age and body weight of patients, the administration mode and time, and the normal daily dosage to a human adult is between about 100 to 3000 mg, optionally divided in one to several times per day. If necessary, the dosage may be increased or decreased appropriately.

Practical and presently preferred embodiments of the invention are illustratively shown in the following Examples, which are not intended to limit the scope of the invention thereto. Further, the abbreviations used therein show the following meanings: PNZ, p-nitrobenzyloxycarbonyl; PNB, p-nitrobenzyl; Ph, phenyl; Ac, acetyl; TBDMS, t-butyldimethylsilyl; Me, methyl.

### Example 1

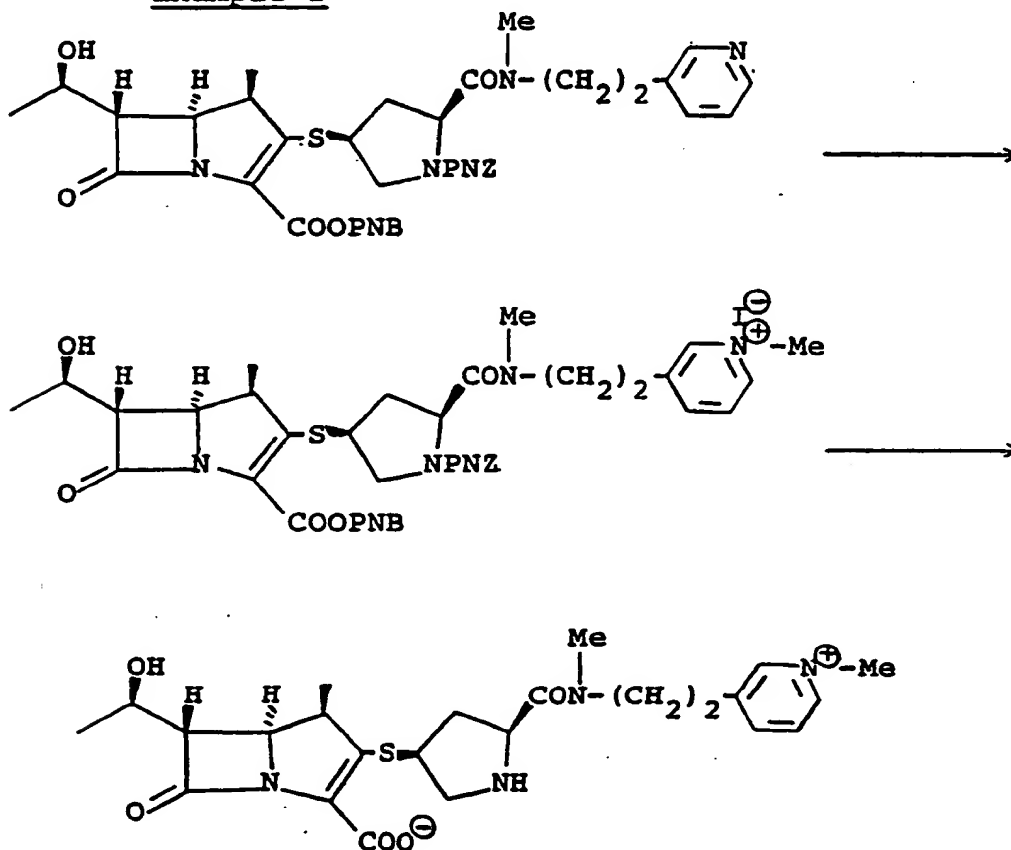


To a solution of (4R,5S,6S,8R,2'S,4'S)-p-nitrobenzyl-3-[1-p-nitrobenzyloxycarbonyl-2-(3-(4-pyridyl)propyl)-methylaminocarbonyl]pyrrolidin-4-ylthio-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-en-7-one-2-carboxylate (100 mg) in acetone (2.0 ml), methyl iodide (1.14 g) was added, and the resultant mixture was

stirred at room temperature for 20 hours, followed by removal of the solvent under reduced pressure. The residue was dissolved in tetrahydrofuran (5.0 ml) and 0.1M phosphate buffer (pH, 7.0; 5.0 ml), and 10 % palladium-carbon (150 mg) was added thereto. Catalytic reduction was performed at room temperature for 1.5 hours under atmospheric pressure of hydrogen. The catalyst was removed by filtration, and the filtrate was washed with dichloromethane three times. After removal of the solvent from the washed filtrate under reduced pressure, the residue was purified by polymer chromatography (CHP-20P) using 2 % aqueous tetrahydrofuran as an eluent. The eluted fractions were collected and freeze-dried to give (4R,5S,6S,8R,2'S,4'S)-3-[2-((3-(1-methylpyridinium-4-yl)propyl)methylaminocarbonyl)pyrrolidin-4-ylthio]-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-en-7-one-2-carboxylate.

UV<sub>max</sub> nm (H<sub>2</sub>O): 257, 263 (sh), 298;  
 IR<sub>max</sub> cm<sup>-1</sup> (KBr): 3400, 1737, 1682, 1367;  
 NMR δ (D<sub>2</sub>O): 1.18 (3H, d, J = 7.3 Hz), 1.26 (3H, d, J = 6.6 Hz), 3.04 (3H, s), 4.20 (3H, s), 7.87 (2H, d, J = 6.6 Hz), 8.60 (2H, d, J = 6.6 Hz).

### Example 2



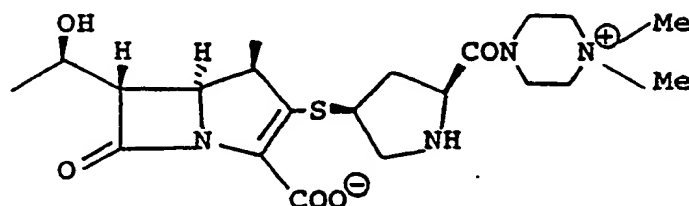
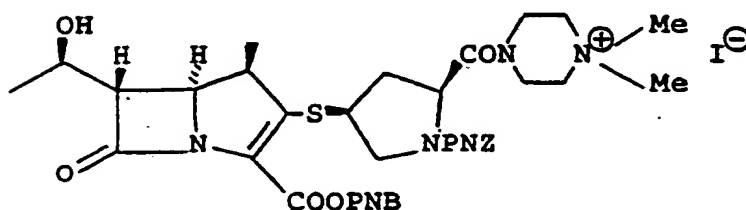
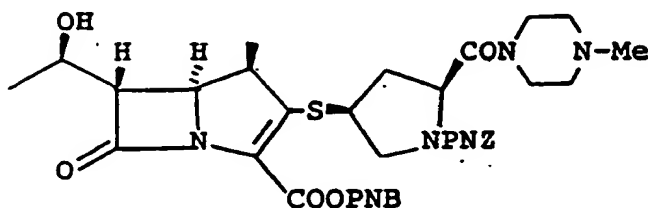
To a solution of (4R,5S,6S,8R,2'S,4'S)-p-nitrobenzyl-3-[1-p-nitrobenzyloxycarbonyl-2-((2-(3-pyridyl)ethyl)methylaminocarbonyl)pyrrolidin-4-ylthio]-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-en-7-one-2-carboxylate (270 mg) in acetone (25 ml), methyl iodide (3.42 g) was added, and the resultant mixture was stirred at room temperature for 3 hours, followed by removal of the solvent under reduced pressure. The residue was dissolved in tetrahydrofuran (15 ml) and 0.1M phosphate buffer (pH, 7.0; 15.0 ml), and 10 % palladium-carbon (500 mg) was added thereto. Catalytic reduction was performed at room temperature for 1 hour under atmospheric pressure of hydrogen. The reaction mixture was subjected to post-treatment in the same manner as in Example 1. The filtrate was purified by polymer chromatography (CHP-20P) using 2 % aqueous tetrahydrofuran as an eluent to give (4R,5S,6S,8R,2'S,4'S)-3-[2-((2-methylpyridinium-3-yl)ethyl)methylaminocarbonyl]pyrrolidin-4-ylthio]-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-en-7-one-2-carboxylate.

UV<sub>max</sub> nm (H<sub>2</sub>O): 268, 273, 298;

IR<sub>max</sub> cm<sup>-1</sup> (KBr): 3320, 1748, 1637, 1585, 1378;

NMR δ (D<sub>2</sub>O): 1.20 (3H, d, J = 7.3 Hz), 1.27 (3H, d, J = 6.3 Hz), 2.81 (1H, m), 3.00 - 3.30 (5H, m), 3.09 (3H, s), 3.45 (3H, m), 3.79 (1H, m), 4.20 (4H, m), 4.38 (3H, s), 7.98 (1H, dd, J = 6.3 and 8.3 Hz), 8.44 (1H, d, J = 8.3 Hz), 8.69 (1H, d, J = 6.3 Hz), 8.79 (1H, s).

### Example 3



To a solution of (4R,5S,6S,8R,2'S,4'S)-p-nitrobenzyl-3-[1-p-nitrobenzyloxycarbonyl-2-(4-methylpiperazin-1-ylcarbonyl)pyrrolidin-4-ylthio]-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-en-7-one-2-carboxylate (200 mg) in acetone (2.0 ml), methyl iodide (1.14 g) was added, and the resultant mixture was stirred at room temperature for 20 hours, followed by removal of the solvent under reduced pressure. The residue was dissolved in tetrahydrofuran (10.0 ml) and 0.1M phosphate buffer (pH, 7.0; 10.0 ml), and 10 % palladium-carbon (241 mg) was added thereto. Catalytic reduction was performed at room temperature for 1.5 hours under atmospheric pressure of hydrogen. The reaction mixture was subjected to post-treatment in the same manner as in Example 1. The filtrate was purified by polymer chromatography (CHP-20P) using 1 % aqueous tetrahydrofuran as an eluent to give (4R,5S,6S,8R,2'S,4'S)-3-[2-(4,4-dimethylpiperazin-1-ylcarbonyl)pyrrolidin-4-ylthio]-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-en-7-one-2-carboxylate.

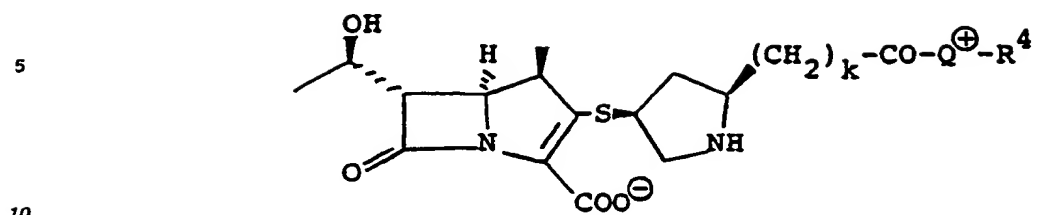
UV<sub>max</sub> nm (H<sub>2</sub>O): 299;

IR<sub>max</sub> cm<sup>-1</sup> (KBr): 3440, 1745, 1640, 1587, 1464, 1387, 1260;

NMR δ (D<sub>2</sub>O): 1.21 (3H, d, J = 7.3 Hz), 1.29 (3H, d, J = 6.6 Hz), 1.72 (1H, m), 2.78 (1H, m), 3.11 (1H, dd, J = 4.0 & 12.5 Hz), 3.27 (6H, s), 3.20 - 3.60 (9H, m), 3.80 - 4.20 (5H, m), 4.23 (3H, m).

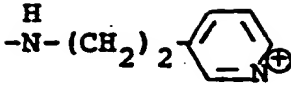

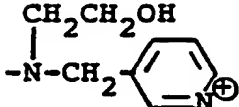

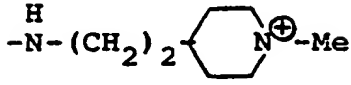
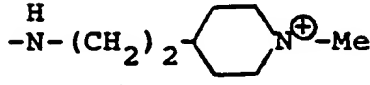
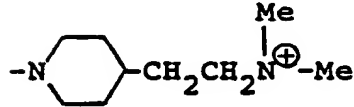
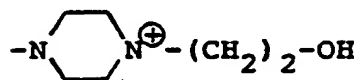
### Examples 4 to 22

In the same manner as above, the compounds as shown in Table 2 were obtained. The physical properties of the compounds as obtained follow the Table.

Table 2

Example No.	k		<u>R<sup>4</sup></u>
4	0		-Me
5	0		-Me
6	0		-Me
7	0		-Me
8	0		-Me
9	0		-Me
10	0		-Me
11	0		-Me
12	0		-Me
13	0		-Me
14	0		-Me



<u>Example No.</u>	<u>k</u>	<u>Q<sup>+</sup></u>	<u>R<sup>4</sup></u>
15	1		-Me
16	2		-Me
17	0		-Me
18	1		-Me
19	0		-Me
20	1		-Me
21	0		-Me
22	0		-Me

45 Physical propertiesExample 4

UV <sub>max</sub> nm (H <sub>2</sub> O):	252, 291;
IR <sub>max</sub> cm <sup>-1</sup> (KBr):	3380, 1737, 1580, 1502, 1364;
NMR δ (D <sub>2</sub> O):	1.19 (3H, d, J = 7.3 Hz), 1.29 (3H, d, J = 6.3 Hz), 1.95 (1H, m), 2.73 (1H, m), 3.00 (1H, dd, J = 4.6 & 11.9 Hz), 3.40 (3H, m), 3.79 (1H, m), 4.09 (1H, dd, J = 5.6 & 9.6 Hz), 4.25 (2H, m), 4.40 (3H, s), 7.99 (1H, dd, J = 6.3 & 8.6 Hz), 8.47 (1H, d, J = 8.6 Hz), 8.53 (1H, d, J = 6.3 Hz), 9.27 (1H, s).

Example 5

UV <sub>max</sub> nm (H <sub>2</sub> O):	265, 273 (sh), 296;
--	---------------------

IR<sub>max</sub> cm<sup>-1</sup> (KBr): 3360, 1730, 1670, 1590, 1385;  
 NMR δ (D<sub>2</sub>O) : 1.19 (3H, d, J = 7.3 Hz), 1.25 (1H, m), 1.27 (3H, d, J = 6.3 Hz), 2.17 (1H, m),  
 3.02 (1H, m), 3.30 - 3.85 (4H, m), 4.08 (1H, m), 4.22 (2H, m), 4.37 (3H, s), 4.65  
 (3H, m), 8.02 (1H, t, J = 7.9 Hz), 8.46 (1H, d, J = 8.3 Hz), 8.71 (1H, d, J = 6.0  
 Hz), 8.77 (1H, s).

Example 6

UV<sub>max</sub> nm (H<sub>2</sub>O): 266, 272, 299;  
 IR<sub>max</sub> cm<sup>-1</sup> (KBr): 3300, 1750, 1652, 1588, 1380, 1366;  
 NMR δ (D<sub>2</sub>O): 1.19 (3H, d, J = 7.3 Hz), 1.29 (3H, d, J = 6.3 Hz), 1.49 (1H, m), 2.69 (1H, m),  
 2.91 (1H, dd, J = 4.5 & 11.9 Hz), 3.10 (2H, t, J = 6.6 Hz), 3.30 - 3.50 (3H, m),  
 3.63 (2H, t, J = 5.9 Hz), 3.75 (1H, m), 3.93 (1H, dd, J = 6.3 & 9.6 Hz), 4.20 -  
 4.30 (2H, m), 4.37 (3H, s), 7.99 (1H, dd, J = 6.2 & 8.0 Hz), 8.44 (1H, d, J = 8.0  
 Hz), 8.67 (1H, d, J = 6.2 Hz), 8.77 (1H, s).

Example 7

UV<sub>max</sub> nm (H<sub>2</sub>O): 266, 273 (sh), 299;  
 IR<sub>max</sub> cm<sup>-1</sup> (KBr): 3410, 1749, 1640, 1588, 1380, 1278, 1255, 1178, 1140;  
 NMR δ (D<sub>2</sub>O): 1.19 (3H, d, J = 7.3 Hz), 1.29 (3H, d, J = 6.3 Hz), 1.75 (1H, m), 1.96 (2H, m),  
 2.69 (1H, m), 2.89 (2H, m), 2.95 (1H, dd, J = 4.3 & 11.9 Hz), 3.20 - 3.50 (5H, m),  
 3.75 (1H, m), 3.87 (1H, dd, J = 6.3 & 9.5 Hz), 4.20 (2H, m), 4.35 (3H, s), 7.94  
 (1H, t, J = 7.0 Hz), 8.38 (1H, d, J = 7.9 Hz), 8.61 (1H, d, J = 6.0 Hz), 8.68 (1H,  
 s).

Example 8

UV<sub>max</sub> nm (H<sub>2</sub>O): 266, 273, 299;  
 NMR δ (D<sub>2</sub>O): 1.19 (3H, d, J = 7.0 Hz), 1.30 (3H, d, J = 6.6 Hz), 1.61 (2H, m), 1.73 (3H, m),  
 2.72 (1H, m), 2.89 (2H, m), 2.99 (1H, dd, J = 4.6 & 11.9 Hz), 3.29 (2H, m), 3.43  
 (3H, m), 3.79 (1H, m), 3.92 (1H, dd, J = 6.3 & 9.2 Hz), 4.23 (2H, m), 4.34 (3H, s),  
 7.93 (1H, dd, J = 6.3 & 8.3 Hz), 8.39 (1H, d, J = 8.3 Hz), 8.59 (1H, d, J = 6.3  
 Hz), 8.68 (1H, s).

Example 9

UV<sub>max</sub> nm (H<sub>2</sub>O): 268, 273, 297;  
 IR<sub>max</sub> cm<sup>-1</sup> (KBr): 3425, 1744, 1632, 1588, 1380, 1281;  
 NMR δ (D<sub>2</sub>O): 1.21 (3H, d, J = 7.3 Hz), 1.30 (3H, d, J = 6.3 Hz), 1.82 (1H, m), 1.98 (2H, m),  
 2.86 (3H, m), 3.09 (3H, s), 3.20 - 3.70 (6H, m), 3.95 (1H, m), 4.24 (2H, m), 4.36  
 (3H, s), 4.48 (1H, dd, J = 6.9 & 9.6 Hz), 7.97 (1H, t, J = 7.0 Hz), 8.42 (1H, d, J  
 = 7.6 Hz), 8.62 (1H, d, J = 6.3 Hz), 8.70 (1H, s).

Example 10

UV<sub>max</sub> nm (H<sub>2</sub>O): 268, 276, 296;  
 IR<sub>max</sub> cm<sup>-1</sup> (KBr): 3425, 1746, 1636, 1592, 1378, 1282, 1246;  
 NMR δ (D<sub>2</sub>O): 1.18 (3H, d, J = 7.3 Hz), 1.28 (3H, d, J = 6.3 Hz), 1.66 (4H, m), 1.86 (1H, m),  
 2.93 (3H, m), 3.03 (3H, s), 3.20 - 3.80 (7H, m), 4.01 (1H, m), 4.23 (2H, m), 4.32  
 (3H, s), 7.92 (1H, t, J = 7.0 Hz), 8.39 (1H, d, J = 7.5 Hz), 8.56 (1H, d, J = 6.2  
 Hz), 8.65 (1H, s).

Example 11

UV<sub>max</sub> nm (H<sub>2</sub>O): 273, 300;  
 IR<sub>max</sub> cm<sup>-1</sup> (KBr): 3400, 1777, 1730, 1618;  
 NMR δ (D<sub>2</sub>O): 1.20 (3H, d, J = 7.3 Hz), 1.28 (3H, d, J = 6.6 Hz), 2.14 (1H, m), 2.68 (1H, m),

2.94 (1H, m), 3.25 - 3.50 (3H, m), 3.63 (1H, dd,  $J = 6.3$  &  $11.9$  Hz), 3.73 (1H, m), 4.02 (1H, m), 4.23 (3H, s), 4.47 (1H, m), 8.10 (2H, d,  $J = 7.3$  Hz), 8.57 (2H, d,  $J = 7.3$  Hz).

5 Example 12

UV<sub>max</sub> nm (H<sub>2</sub>O): 258, 263 (sh), 297;  
 IR<sub>max</sub> cm<sup>-1</sup> (KBr): 3420, 1743, 1638, 1582, 1381;  
 NMR  $\delta$  (D<sub>2</sub>O): 1.19 (3H, d,  $J = 7.3$  Hz), 1.28 (3H, d,  $J = 6.6$  Hz), 1.91 (1H, m), 2.76 (1H, m),  
 10 3.06 (1H, dd,  $J = 4.0$  &  $11.9$  Hz), 3.43 (3H, m), 3.80 (1H, m), 4.10 (1H, dd,  $J = 5.9$  &  $9.7$  Hz), 4.21 (2H, m), 4.34 (3H, s), 4.68 (1H, d,  $J = 18.2$  Hz), 4.70 (1H, d,  $J = 18.2$  Hz), 7.90 (2H, d,  $J = 6.3$  Hz), 8.69 (2H, d,  $J = 6.3$  Hz).

15 Example 13

UV<sub>max</sub> nm (H<sub>2</sub>O): 256, 263, 299;  
 IR<sub>max</sub> cm<sup>-1</sup> (KBr): 3410, 1743, 1639, 1584, 1376;  
 NMR  $\delta$  (D<sub>2</sub>O): 1.20 (3H, d,  $J = 7.3$  Hz), 1.31 (3H, d,  $J = 6.3$  Hz), 1.79 (1H, m), 2.01 (2H, m),  
 20 2.72 (1H, m), 2.99 (3H, m), 3.20 - 3.50 (5H, m), 3.79 (1H, m), 3.92 (1H, m), 4.30 (2H, m), 4.33 (3H, s), 7.89 (2H, d,  $J = 6.6$  Hz), 8.62 (2H, d,  $J = 6.6$  Hz).

Example 14

UV<sub>max</sub> nm (H<sub>2</sub>O): 257, 263 (sh), 300;  
 25 NMR  $\delta$  (D<sub>2</sub>O): 1.18 (3H, d,  $J = 7.3$  Hz), 1.26 (3H, d,  $J = 6.3$  Hz), 1.80 (1H, m), 2.77 (1H, m), 3.05 (3H, s), 4.28 (3H, s), 7.93 (2H, d,  $J = 6.6$  Hz), 8.64 (2H, d,  $J = 6.6$  Hz).

Example 15

30 UV<sub>max</sub> nm (H<sub>2</sub>O): 269, 273, 296;  
 IR<sub>max</sub> cm<sup>-1</sup> (KBr): 3380, 1742, 1652, 1580, 1370, 1239, 1008;  
 NMR  $\delta$  (D<sub>2</sub>O): 1.18 (3H, d,  $J = 6.9$  Hz), 1.26 (3H, d,  $J = 6.3$  Hz), 1.92 (1H, m), 2.42 (1H, m),  
 35 2.56 (2H, m), 3.04 (3H, m), 3.25 - 3.70 (5H, m), 3.80 (1H, m), 3.96 (1H, m), 4.26 (2H, m), 4.35 (3H, s), 7.95 (1H, t,  $J = 7.6$  Hz), 8.40 (1H, d,  $J = 8.6$  Hz), 8.65 (1H, d,  $J = 6.0$  Hz), 8.72 (1H, s).

Example 16

40 UV<sub>max</sub> nm (H<sub>2</sub>O): 249, 294;  
 NMR  $\delta$  (D<sub>2</sub>O): 1.21 (3H, d,  $J = 6.9$  Hz), 1.29 (3H, d,  $J = 6.3$  Hz), 1.70 (1H, m), 2.15 (2H, m), 2.73 (2H, m), 3.20 - 3.50 (3H, m), 3.50 - 3.85 (3H, m), 4.10 (1H, m), 4.18 (2H, m), 4.38 (3H, s), 7.92 (1H, m), 8.37 (1H, d,  $J = 7.9$  Hz), 8.51 (1H, d,  $J = 5.9$  Hz), 9.27 (1H, s).

45 Example 17

UV<sub>max</sub> nm (H<sub>2</sub>O): 267, 272, 300;  
 IR<sub>max</sub> cm<sup>-1</sup> (KBr): 3410, 1746, 1638, 1586, 1383;  
 NMR  $\delta$  (D<sub>2</sub>O): 1.22 (3H, d,  $J = 7.3$  Hz), 1.30 (3H, d,  $J = 6.3$  Hz), 1.70 (1H, m), 2.85 (1H, m),  
 50 3.12 (1H, dd,  $J = 3.6$  &  $12.2$  Hz), 3.25 (1H, dd,  $J = 5.3$  &  $12.2$  Hz), 3.43 (2H, m), 3.70 - 3.90 (5H, m), 4.24 (2H, m), 4.39 (1H, m), 4.40 (3H, s), 4.80 (1H, d,  $J = 16.5$  Hz), 4.92 (1H, d,  $J = 16.5$  Hz), 8.03 (1H, dd,  $J = 6.5$  &  $7.9$  Hz), 8.43 (1H, d,  $J = 7.9$  Hz), 8.71 (2H, m).

55 Example 18

UV<sub>max</sub> nm (H<sub>2</sub>O): 297;  
 IR<sub>max</sub> cm<sup>-1</sup> (KBr): 3400, 1748, 1639, 1586, 1453, 1372, 1257, 1088;

NMR  $\delta$  (D<sub>2</sub>O): 1.17 (3H, d, J = 7.3 Hz), 1.24 (3H, d, J = 6.3 Hz), 1.49 (1H, m), 2.61 (1H, m), 2.90 (2H, d, J = 6.9 Hz), 3.08 (1H, dd, J = 3.3 & 12.5 Hz), 3.21 (6H, s), 3.30 - 3.60 (7H, m), 3.73 (1H, t, J = 7.3 Hz), 3.90 (5H, m), 4.20 (2H, m).

5 Example 19

UV<sub>max</sub> nm (H<sub>2</sub>O): 300;  
 IR<sub>max</sub> cm<sup>-1</sup> (KBr): 3410, 1744, 1650, 1588, 1485, 1381, 1250, 1206, 1092;  
 10 NMR  $\delta$  (D<sub>2</sub>O): 1.22 (3H, d, J = 7.0 Hz), 1.31 (3H, d, J = 6.3 Hz), 1.70 (6H, m), 2.00 (2H, m), 2.74 (1H, m), 3.04 (1H, dd, J = 5.0 & 12.2 Hz), 3.08 (3H, s), 3.15 (3H, s), 3.25 - 3.60 (9H, m), 3.81 (1H, m), 3.97 (1H, dd, J = 6.4 & 9.5 Hz), 4.24 (2H, m).

Example 20

15 UV<sub>max</sub> nm (H<sub>2</sub>O): 297;  
 IR<sub>max</sub> cm<sup>-1</sup> (KBr): 3400, 1742, 1635, 1582, 1479, 1363, 1241, 1201, 1082;  
 NMR  $\delta$  (D<sub>2</sub>O): 1.28 (3H, d, J = 7.3 Hz), 1.30 (3H, d, J = 6.3 Hz), 1.70 (6H, m), 1.97 (2H, m), 2.72 (1H, m), 2.79 (1H, m), 3.08 (3H, s), 3.15 (3H, s), 3.23 - 3.70 (10H, m), 4.02 (2H, m), 4.31 (2H, m).

20

Example 21

UV<sub>max</sub> nm (H<sub>2</sub>O): 295;  
 IR<sub>max</sub> cm<sup>-1</sup> (KBr): 3440, 1758, 1644, 1597, 1492, 1379, 1258;  
 25 NMR  $\delta$  (D<sub>2</sub>O): 1.21 (3H, d, J = 7.0 Hz), 1.29 (3H, d, J = 6.6 Hz), 1.80 (7H, m), 2.86 (1H, m), 3.02 (1H, m), 3.11 (9H, s), 3.18 (2H, m), 3.39 (5H, m), 3.60 (1H, m), 3.80 (1H, m), 3.99 (1H, m), 4.24 (2H, m), 4.34 (1H, m), 4.64 (1H, m).

Example 22

30 UV<sub>max</sub> nm (H<sub>2</sub>O): 297;  
 IR<sub>max</sub> cm<sup>-1</sup> (KBr): 3400, 1743, 1637, 1588, 1380;  
 NMR  $\delta$  (D<sub>2</sub>O): 1.22 (3H, d, J = 6.9 Hz), 1.30 (3H, d, J = 6.3 Hz), 1.68 (1H, m), 3.10 (1H, dd, J = 4.0 & 12.5 Hz), 2.76 (1H, m), 3.24 (1H, dd, J = 5.4 & 12.5 Hz), 3.31 (3H, s), 3.43 (2H, m), 3.68 (8H, m), 3.86 (1H, m), 3.97 (2H, m), 4.12 (2H, m), 4.25 (3H, m).

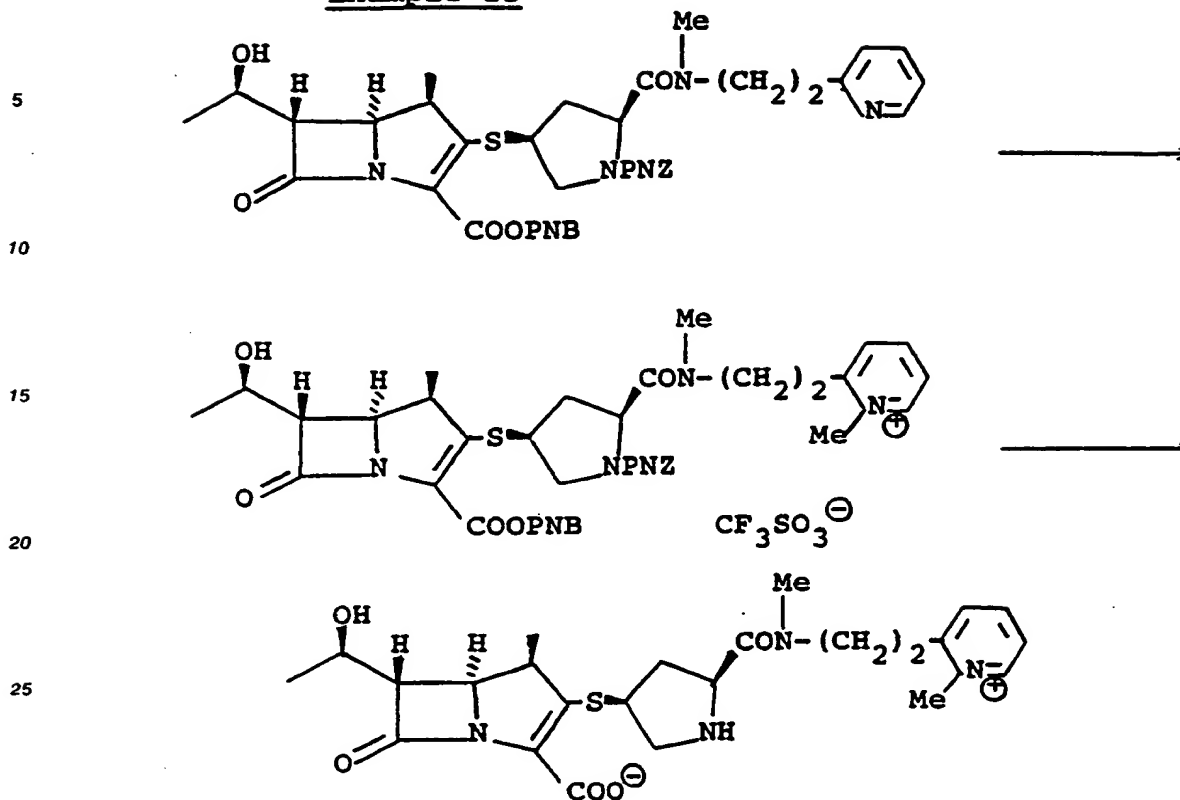
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Example 23

A solution of (4R,5S,6S,8R,2'S,4'S)-p-nitrobenzyl-3-[1-(p-nitrobenzyloxycarbonyl-2-((2-(2-pyridyl)ethyl)-methylaminocarbonyl)pyrrolidin-4-ylthio)-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-en-7-one-2-carboxylate (208 mg) in dry dichloromethane (3.0 ml) was stirred under ice-cooling, and methyl trifluoromethanesulfonate (64 mg) was dropwise added thereto, followed by stirring at the same temperature for 1 hour. The reaction mixture was combined with tetrahydrofuran (10.0 ml), 0.1M phosphate buffer (pH, 7.0; 10.0 ml) and 10 % palladium-carbon (350 mg), and catalytic reduction was performed at room temperature for 1 hour under atmospheric pressure of hydrogen. The reaction mixture was subjected to post-treatment in the same manner as in Example 1. The filtrate was purified by polymer chromatography (CHP-20P) using 2 % aqueous tetrahydrofuran as an eluent to give (4R,5S,6S,8R,2'S,4'S)-3-[2-((2-(1-methylpyridinium-2-yl)ethyl)methylaminocarbonyl)pyrrolidin-4-ylthio]-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-en-7-one-2-carboxylate.

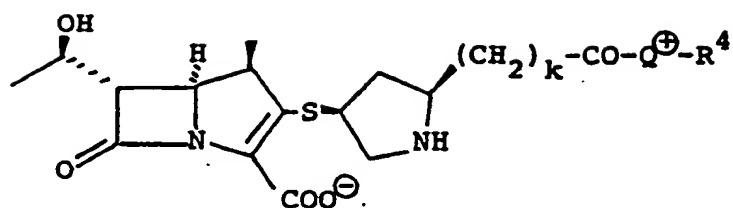
UV<sub>max</sub> nm (H<sub>2</sub>O): 269, 274, 298;

IR<sub>max</sub> cm<sup>-1</sup> (KBr): 3450, 1737, 1625, 1580, 1372, 1251, 1153;

NMR δ (D<sub>2</sub>O): 1.20 (3H, d, J = 7.2 Hz), 1.28 (3H, d, J = 6.3 Hz), 1.60 (1H, m), 3.00 (1H, m), 3.16 (3H, s), 3.26 (1H, dd, J = 3.3 & 12.2 Hz), 3.30 - 3.60 (5H, m), 3.65 (1H, m), 3.94 (1H, m), 4.13 (1H, m), 4.23 (2H, m), 4.40 (3H, s), 4.52 (1H, dd, J = 7.2 & 9.9 Hz), 7.90 (1H, d, J = 7.9 Hz), 7.92 (1H, t, J = 6.0 Hz), 8.45 (1H, t, J = 7.9 Hz), 8.76 (1H, d, J = 6.0 Hz).

50 Examples 24 to 31

In the same manner as in Example 23, the compounds as shown in Table 3 were obtained. The physical properties of the compounds as obtained follow the Table.

Table 3

<u>Example No.</u>	<u>k</u>	<u>Q<sup>+</sup></u>	<u>R<sup>4</sup></u>
15 24	0		-Me
20 25	0		-Me
25 26	0		-Me
30 27	0		-Me
35 28	0		-Me
40 29	0		-Me
45 30	0		-Me
50 31	0		-Me

55 Physical propertiesExample 24

UV<sub>max</sub> nm (H<sub>2</sub>O): 267, 274 (sh), 298;  
 IR<sub>max</sub> cm<sup>-1</sup> (KBr): 3430, 1743, 1679, 1577, 1380, 1260, 1158;  
 NMR δ (D<sub>2</sub>O): 1.21 (3H, d, J = 7.3 Hz), 1.28 (3H, d, J = 6.3 Hz), 2.20 (1H, m), 3.03 (1H, m),  
 3.03 - 3.60 (3H, m), 3.76 (1H, dd, J = 6.3 & 12.2 Hz), 4.07 (1H, m), 4.23 (2H, m),  
 4.34 (3H, s), 4.64 (1H, dd, J = 6.6 & 8.9 Hz), 4.89 (1H, d, J = 18.2 Hz), 4.90 (1H,  
 d, J = 18.2 Hz), 7.95 (1H, t, J = 7.0 Hz) 7.96 (1H, d, J = 8.0 Hz), 8.52 (1H, t, J  
 = 8.0 Hz), 8.79 (1H, d, J = 6.3 Hz).

Example 25

UV<sub>max</sub> nm (H<sub>2</sub>O): 268, 273 (sh), 297;  
 IR<sub>max</sub> cm<sup>-1</sup> (KBr): 3440, 1750, 1672, 1630, 1580, 1379, 1270;  
 NMR δ (D<sub>2</sub>O): 1.19 (3H, d, J = 7.3 Hz), 1.28 (3H, d, J = 6.3 Hz), 1.88 (1H, m), 2.89 (1H, m),  
 3.30 - 3.50 (5H, m), 3.70 (2H, m), 3.85 (1H, dd, J = 6.9 & 14.2 Hz), 4.00 (1H, m),  
 4.24 (2H, m), 4.36 (3H, s), 4.41 (1H, dd, J = 6.6 & 9.6 Hz), 7.90 (2H, m), 8.46  
 (1H, t, J = 6.6 Hz), 8.76 (1H, d, J = 6.1 Hz).

Example 26

UV<sub>max</sub> nm (H<sub>2</sub>O): 267, 273 (sh), 296;  
 IR<sub>max</sub> cm<sup>-1</sup> (KBr): 3450, 1745, 1640, 1584, 1380, 1255, 1159;  
 NMR δ (D<sub>2</sub>O): 1.21 (3H, d, J = 6.9 Hz), 1.30 (3H, d, J = 6.3 Hz), 2.03 (1H, m), 2.14 (2H, m),  
 3.20 - 3.30 (3H, m), 3.19 (3H, s), 3.30 - 3.70 (4H, m), 3.80 (2H, m), 4.10 (1H, m),  
 4.28 (2H, m), 4.30 (3H, s), 7.86 (1H, t, J = 6.6 Hz), 7.98 (1H, d, J = 8.3 Hz), 8.45  
 (1H, t, J = 7.6 Hz), 8.72 (1H, d, J = 5.6 Hz).

Example 27

UV<sub>max</sub> nm (H<sub>2</sub>O): 296, 270 (sh), 265;  
 IR<sub>max</sub> cm<sup>-1</sup> (KBr): 3430, 1740, 1669, 1578, 1441, 1378, 1267, 1246, 1157;  
 NMR δ (D<sub>2</sub>O): 1.21 (3H, d, J = 7.2 Hz), 1.30 (3H, d, J = 6.6 Hz), 1.78 (1H, m), 2.75 (3H, s),  
 2.90 (1H, m), 3.09 (2H, m), 3.30 - 3.60 (5H, m), 3.68 (1H, dd, J = 6.0 & 12.2 Hz),  
 3.79 (1H, m), 4.01 (1H, m), 4.21 (3H, s), 4.23 (2H, m), 4.42 (1H, dd, J = 6.0 & 9.6  
 Hz), 7.87 (1H, d, J = 7.9 Hz), 8.30 (1H, dd, J = 1.3 & 7.9 Hz), 8.68 (1H, d, J =  
 1.3 Hz).

Example 28

UV<sub>max</sub> nm (H<sub>2</sub>O): 278, 296;  
 IR<sub>max</sub> cm<sup>-1</sup> (KBr): 3430, 1753, 1677, 1592, 1450, 1382, 1278, 1254, 1224, 1156;  
 NMR δ (D<sub>2</sub>O): 1.22 (3H, d, J = 7.3 Hz), 1.30 (3H, d, J = 6.6 Hz), 1.81 (1H, m), 2.83 (3H, s),  
 2.89 (1H, m), 3.17 (2H, m), 3.38 (2H, m), 3.50 (2H, m), 3.72 (2H, m), 4.00 (1H, m),  
 4.24 (2H, m), 4.28 (3H, s), 4.39 (1H, dd, J = 6.6 & 9.3 Hz), 7.80 (1H, t, J = 7.2  
 Hz), 8.29 (1H, d, J = 7.6 Hz), 8.63 (1H, d, J = 5.3 Hz).

Example 29

UV<sub>max</sub> nm (H<sub>2</sub>O): 300, 264, 257, 228;  
 IR<sub>max</sub> cm<sup>-1</sup> (KBr): 3400 (br), 1746, 1640, 1582, 1381, 1266;  
 NMR δ (D<sub>2</sub>O): 1.21 (3H, d, J = 7.3 Hz), 1.30 (3H, d, J = 6.3 Hz), 1.56 (1H, m), 2.73 (1H, m),  
 2.97 (1H, dd, J = 4.8 & 12.2 Hz), 3.20 (2H, m), 3.40 (3H, m), 3.75 (1H, m), 4.00  
 (1H, dd, J = 6.0 & 9.6 Hz) 4.24 (3H, m), 4.34 (3H, s), 7.95 (2H, d, J = 6.6 Hz),  
 8.69 (2H, d, J = 6.6 Hz).

Example 30

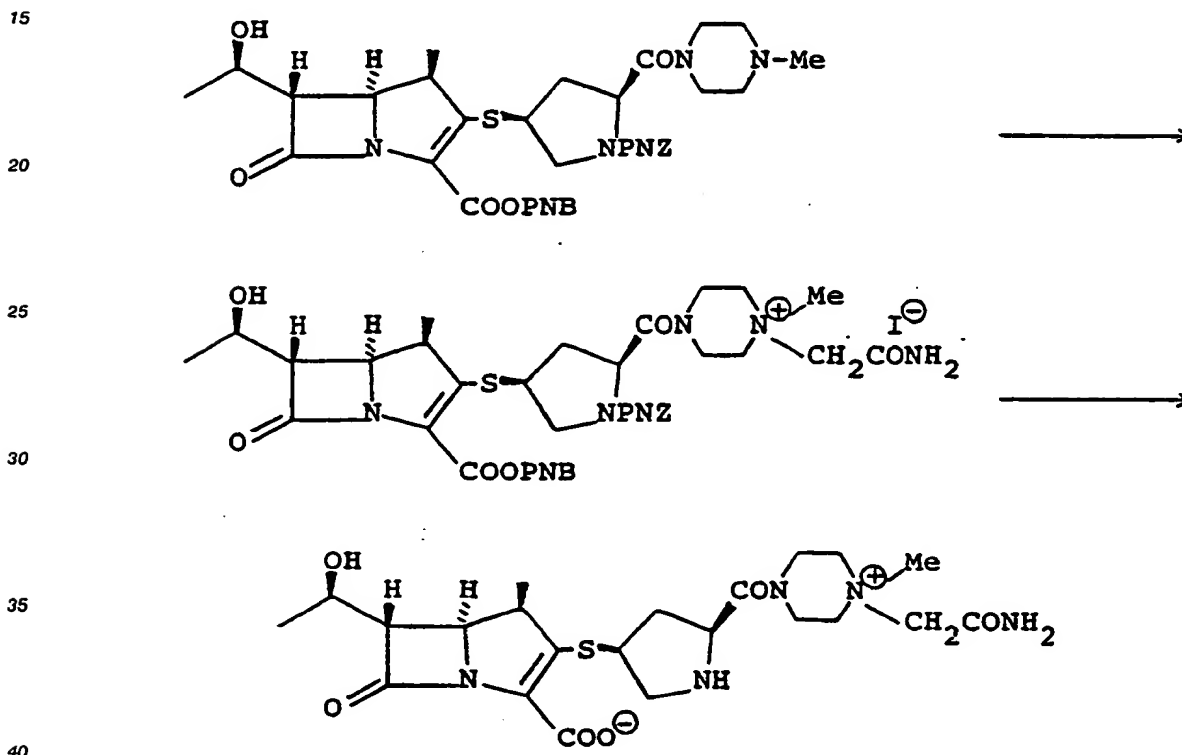
UV<sub>max</sub> nm (H<sub>2</sub>O): 294;  
 IR<sub>max</sub> cm<sup>-1</sup> (KBr): 3400, 1749, 1640, 1588, 1382, 1252;

NMR  $\delta$  (D<sub>2</sub>O): 1.22 (3H, d, J = 7.3 Hz), 1.31 (3H, d, J = 6.6 Hz), 1.76 (1H, m), 2.10 (2H, m), 2.81 (1H, m), 3.20 (2H, m), 3.24 (3H, s), 3.43 (1H, m), 3.61 (7H, m), 3.73 (2H, m), 3.92 (3H, m), 4.27 (5H, m).

### 5 Example 31

UV<sub>max</sub> nm (H<sub>2</sub>O): 292;  
 IR<sub>max</sub> cm<sup>-1</sup> (KBr): 3430, 1752, 1640, 1592, 1390, 1260;  
 NMR  $\delta$  (D<sub>2</sub>O): 1.24 (3H, d, J = 7.3 Hz), 1.32 (3H, d, J = 6.3 Hz), 1.69 (1H, m), 2.80 (1H, m),  
 10 3.12 (1H, dd, J = 3.3 & 12.9 Hz), 3.24 (1H, dd, J = 5.0 & 12.9 Hz), 3.31 (3H, s),  
 3.43 (3H, s), 3.44 (2H, m), 3.52 - 4.10 (13H, m), 4.29 (3H, m).

### Example 32



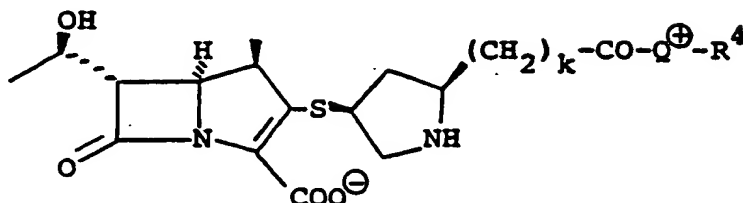
To a solution of (4R,5S,6S,8R,2'S,4'S)-p-nitrobenzyl-3-[1-p-nitrobenzyloxycarbonyl-2-(4-methylpiperazin-1-ylcarbonyl)pyrrolidin-4-ylthio]-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-en-7-one-2-carboxylate (200 mg) in acetone (3.0 ml), iodoacetamide (200 mg) was added at room temperature, and the resultant mixture was stirred at the same temperature for 20 hours and concentrated under reduced pressure. The residue was combined with ethyl acetate (20 ml), stirred and allowed to stand. After removal of the supernatant by decantation, the insoluble material was dissolved in tetrahydrofuran (10 ml) and 0.1M phosphate buffer (pH, 7.0; 10 ml), followed by addition of 10 % palladium-carbon (430 mg). Catalytic reduction was performed at room temperature for 2 hours under ordinary or autogenic pressure. The reaction mixture was subjected to post-treatment in the same manner as in Example 1. The filtrate was purified by polymer chromatography (CHP-20P) using 1 % aqueous tetrahydrofuran as an eluent to give (4R,5S,6S,8R,2'S,4'S)-3-[2-(4-aminocarbonylmethyl)-4-methylpiperazin-1-ylcarbonyl]pyrrolidin-4-ylthio]-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-en-7-one-2-carboxylate.

UV<sub>max</sub> nm (H<sub>2</sub>O): 297;  
 IR<sub>max</sub> cm<sup>-1</sup> (KBr): 3400, 1740, 1692, 1652, 1441, 1400, 1253, 1177, 1136;  
 NMR  $\delta$  (D<sub>2</sub>O): 1.23 (3H, d, J = 7.3 Hz), 1.29 (3H, d, J = 6.3 Hz), 2.05 (1H, m), 3.10 (1H, m),  
 3.45 (3H, s), 3.48 (3H, m), 3.70 - 4.40 (13H, m).



Examples 33 to 37

In the same manner as in Example 32, the compounds as shown in Table 4 were obtained. The physical properties of the compounds obtained follow the Table.

Table 4

<u>Example No.</u>	<u>k</u>	<u>Q<sup>+</sup></u>	<u>R<sup>4</sup></u>
33	0		-CH <sub>2</sub> CONH <sub>2</sub>
34	0		-CH <sub>2</sub> CONH <sub>2</sub>
35	0		-CH <sub>2</sub> CONH <sub>2</sub>
36	1		-CH <sub>2</sub> CONH <sub>2</sub>
37	0		-CH <sub>2</sub> CONH <sub>2</sub>

Physical propertiesExample 33

UV <sub>max</sub> nm (H <sub>2</sub> O):	273, 294;
IR <sub>max</sub> cm <sup>-1</sup> (KBr):	3380, 1742, 1677, 1580, 1434, 1380, 1275, 1242;
NMR δ (D <sub>2</sub> O):	1.20 (3H, d, J = 7.3 Hz), 1.29 (3H, d, J = 6.3 Hz), 1.77 (1H, m), 2.80 (1H, m), 3.14 (2H, m), 3.33 (2H, m), 3.45 (1H, dd, J = 2.6 & 6.3 Hz), 3.50 - 3.75 (2H, m), 3.78 (1H, dd, J = 6.3 & 13.5 Hz), 4.20 - 4.40 (3H, m), 5.50 (2H, s), 8.09 (1H, dd, J = 6.3 & 8.3 Hz), 8.58 (1H, d, J = 8.3 Hz), 8.70 (1H, d, J = 6.3 Hz), 8.78 (1H, s).

Example 34

	UV <sub>max</sub> nm (H <sub>2</sub> O):	271, 294;
	IR <sub>max</sub> cm <sup>-1</sup> (KBr):	3390, 1751, 1693, 1638, 1592, 1378;
5	NMR δ (D <sub>2</sub> O):	1.20 (3H, d, J = 7.3 Hz), 1.28 (3H, J = 6.3 Hz), 1.54 (1H, m), 3.02 (1H, m), 3.03 (3H, s), 3.22 (2H, m), 3.36 (2H, m), 3.46 (1H, dd, J = 2.6 & 5.9 Hz), 3.61 (2H, m), 3.97 (1H, m), 4.12 (1H, m), 4.24 (2H, m), 4.74 (1H, m), 5.50 (2H, s), 8.08 (1H, dd, J = 6.3 & 8.2 Hz), 8.60 (1H, d, J = 8.2 Hz), 8.71 (1H, d, J = 6.3 Hz), 8.79 (1H, s).

Example 35

10	UV <sub>max</sub> nm (H <sub>2</sub> O):	259, 265 (sh), 297;
	IR <sub>max</sub> cm <sup>-1</sup> (KBr):	3400, 1748, 1682, 1639, 1545, 1388, 1279;
15	NMR δ (D <sub>2</sub> O):	1.23 (3H, d, J = 7.3 Hz), 1.29 (3H, d, J = 6.3 Hz), 2.28 (1H, m), 3.05 (1H, m), 3.35 - 3.60 (3H, m), 3.84 (1H, dd, J = 7.3 & 12.2 Hz), 4.10 - 4.45 (3H, m), 5.51 (2H, s), 8.02 (2H, d, J = 7.0 Hz) 8.75 (2H, d, J = 7.0 Hz).

Example 36

20	UV <sub>max</sub> nm (H <sub>2</sub> O):	297;
	IR <sub>max</sub> cm <sup>-1</sup> (KBr):	3380, 1747, 1687, 1636, 1586, 1444, 1378, 1244, 1089;
	NMR δ (D <sub>2</sub> O):	1.17 (3H, d, J = 7.3 Hz), 1.24 (3H, d, J = 6.3 Hz), 1.54 (1H, m), 2.63 (1H, m), 2.93 (2H, br.d, J = 6.6 Hz), 3.12 (1H, br.d, J = 12.5 Hz), 3.37 (3H, s), 4.23 (4H, m).

Example 37

25	UV <sub>max</sub> nm (H <sub>2</sub> O):	299, 263 (sh), 256, 226 (sh);
	IR <sub>max</sub> cm <sup>-1</sup> (KBr):	3400, 1746, 1691, 1637, 1584, 1387;
30	NMR δ (D <sub>2</sub> O):	1.22 (3H, d, J = 7.3 Hz), 1.31 (3H, d, J = 6.3 Hz), 1.62 (1H, m), 2.13 (2H, m), 2.86 (1H, m), 3.03 (2H, m), 3.08 (3H, s), 3.22 (2H, m), 3.45 (3H, m), 3.66 (1H, m), 3.87 (1H, m), 4.28 (3H, m), 5.52 (2H, s), 8.00 (2H, d, J = 6.9 Hz), 8.68 (2H, d, J = 6.9 Hz).

Examples 38 to 47

35 In the same manner as in Example 32 but using different alkylating agents (Y) in place of iodoacetamide, the compounds as shown in Table 5 were obtained. The physical properties of the compounds obtained follow the Table.

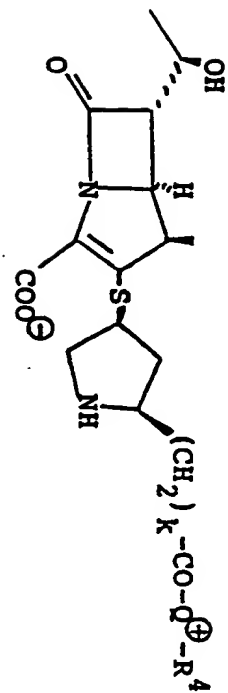
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Table 5



Example No.	$\underline{Y}$	$\underline{k}$	$\underline{Q^+}$	$\underline{R^4}$
38	$\text{BrCH}_2\text{CONH-Me}$	0		$-\text{CH}_2\text{CONH-Me}$
39	$\text{BrCH}_2\text{CON-Me}$	0		$-\text{CH}_2\text{CON-Me}$
40	$\text{ICH}_2\text{CH}_2\text{CON-Me}$	0		$-\text{CH}_2\text{CH}_2\text{CON-Me}$
41	$\text{BrCH}_2\text{COOPNB}$	0		$-\text{CH}_2\text{COOH}$
42	$\text{ICH}_2\text{COOH}$	0		$-\text{CH}_2\text{COOH}$

Example No.	$\underline{Y}$	$\underline{K}$	$\underline{Q^+}$	$\underline{R^4}$
43	$\text{PhCH}_2\text{Br}$	0		$-\text{CH}_2\text{Ph}$
44	$\text{BrCH}_2\text{COMe}$	0		$-\text{CH}_2\text{COMe}$
45	$\text{ICH}_2\text{CH}_2\text{OH}$	0		$-\text{CH}_2\text{CH}_2\text{OH}$
46	$\text{BrCH}_2\text{CO-Me}$	0		$-\text{CH}_2\text{CO-Me}$
47	$\text{BrCH}_2\text{COOPNB}$	0		$-\text{CH}_2\text{COOH}$

Physical propertyExample 38UV<sub>max</sub> nm (H<sub>2</sub>O):

299;

IR<sub>max</sub> cm<sup>-1</sup> (KBr):

3410, 1736, 1638, 1362;

NMR δ (D<sub>2</sub>O):

1.19 (3H, d, J = 7.3 Hz), 1.26 (3H, d, J = 6.3 Hz), 2.77 (3H, s), 3.15 (1H, dd, J = 3.3 &amp; 12.2 Hz), 3.28 (1H, dd, J = 4.4 &amp; 12.2 Hz), 3.38 (3H, s).

Example 39

5      UV<sub>max</sub> nm (H<sub>2</sub>O):      296;  
         IR<sub>max</sub> cm<sup>-1</sup> (KBr):    3400, 1746, 1644, 1589, 1378, 1253;  
         NMR δ (D<sub>2</sub>O):        1.22 (3H, d, J = 7.3 Hz), 1.30 (3H, d, J = 6.3 Hz), 1.71 (1H, m), 2.78 (1H, m),  
    2.98 (3H, s), 3.05 (3H, s), 3.13 (1H, dd, J = 3.6 & 12.2 Hz), 3.25 (1H, dd, J = 4.0  
    & 12.2 Hz), 3.46 (3H, s), 4.53 (2H, br. s).

Example 40

10      UV<sub>max</sub> nm (H<sub>2</sub>O):      297;  
         IR<sub>max</sub> cm<sup>-1</sup> (KBr):    3430, 1745, 1633, 1583, 1480, 1369, 1242, 1087;  
         NMR δ (D<sub>2</sub>O):        1.22 (3H, d, J = 7.3 Hz), 1.31 (3H, d, J = 6.6 Hz), 1.93 (1H, m), 2.96 (3H, s),  
    3.11 (3H, s), 3.26 (3H, s).

Example 41

15      UV<sub>max</sub> nm (H<sub>2</sub>O):      298;  
         IR<sub>max</sub> cm<sup>-1</sup> (KBr):    3420, 1745, 1627, 1592, 1448, 1382, 1254;  
         NMR δ (D<sub>2</sub>O):        1.23 (3H, d, J = 7.3 Hz), 1.30 (3H, d, J = 6.3 Hz), 1.82 (1H, m), 2.92 (1H, m),  
    3.42 (3H, s).

Example 42

20      UV<sub>max</sub> nm (H<sub>2</sub>O):      258, 266 (sh), 292;  
         NMR δ (D<sub>2</sub>O):        1.22 (3H, d, J = 7.3 Hz), 1.29 (3H, d, J = 6.3 Hz), 2.21 (1H, m), 3.01 (1H, m),  
 25      3.38 (1H, m), 3.49 (3H, m), 3.79 (1H, dd, J = 6.6 & 12.2 Hz), 4.10 (1H, m), 4.26  
    (2H, m), 4.66 (2H, m), 5.21 (2H, s), 7.97 (2H, d, J = 6.9 Hz), 8.71 (2H, d, J = 6.9  
    Hz).

Example 43

30      UV<sub>max</sub> nm (H<sub>2</sub>O):      261, 266, 298;  
         IR<sub>max</sub> cm<sup>-1</sup> (KBr):    3400, 1753, 1672, 1596, 1367;  
         NMR δ (D<sub>2</sub>O):        1.15 (3H, d, J = 7.3 Hz), 1.30 (3H, d, J = 6.6 Hz), 1.85 (1H, m), 2.72 (1H, m),  
 35      3.10 - 4.00 (5H, m), 4.25 (3H, m), 4.59 (1H, d, J = 15.9 Hz), 4.68 (1H, d, J =  
    15.9 Hz), 5.84 (2H, s), 7.60 (5H, m), 8.07 (1H, t, J = 7.9 Hz), 8.51 (1H, d, J = 8.5  
    Hz), 8.81 (1H, s), 8.87 (1H, d, J = 5.9 Hz).

Example 44

40      UV<sub>max</sub> nm (H<sub>2</sub>O):      299, 264 (sh), 257, 230;  
         IR<sub>max</sub> cm<sup>-1</sup> (KBr):    3410 (br), 1745, 1638, 1593, 1378;  
         NMR δ (D<sub>2</sub>O):        1.22 (3H, d, J = 7.6 Hz), 1.31 (3H, d, J = 6.3 Hz), 1.66 (1H, m), 2.16 (2H, m),  
    2.44 (3H, s), 2.90 (1H, m), 3.07 (3H, s), 3.68 (1H, m), 3.87 (1H, m), 4.27 (4H, m),  
    8.00 (2H, d, J = 6.9 Hz), 8.53 (2H, d, J = 6.9 Hz).

Example 45

50      UV<sub>max</sub> nm (D<sub>2</sub>O):      296, 261, 255, 223;  
         IR<sub>max</sub> cm<sup>-1</sup> (KBr):    3425, 1751, 1639, 1592, 1304;  
         NMR δ (D<sub>2</sub>O):        1.23 (3H, d, J = 7.3 Hz), 1.32 (3H, d, J = 6.3 Hz), 1.62 (1H, m), 2.12 (2H, m),  
    2.86 (1H, m), 2.97 (2H, m), 3.09 (3H, s), 3.20 (2H, m), 3.44 (4H, m), 3.62 (1H, m),  
    3.90 (1H, m), 4.08 (2H, m), 4.26 (4H, m), 7.97 (2H, d, J = 6.6 Hz), 8.72 (2H, d, J  
    = 6.6 Hz).

Example 46

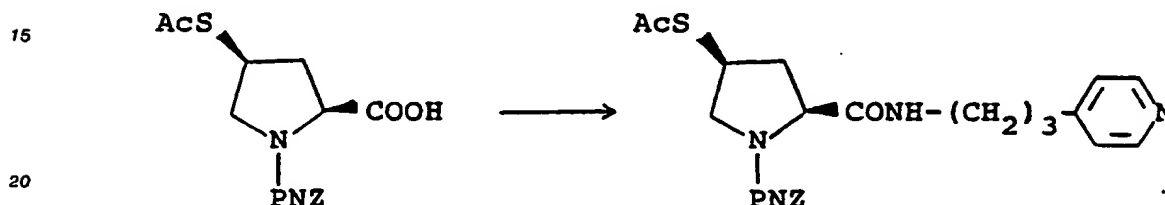
55      UV<sub>max</sub> nm (H<sub>2</sub>O):      296;  
         IR<sub>max</sub> cm<sup>-1</sup> (KBr):    3400 (br), 1743, 1724, 1630, 1593, 1380, 1251;

NMR  $\delta$  (D<sub>2</sub>O): 1.20 (3H, d, J = 7.3 Hz), 1.28 (3H, d, J = 6.3 Hz), 1.70 (1H, m), 2.26 (3H, s), 2.77 (1H, m), 3.07 (1H, dd, J = 12.5 & 3.6 Hz), 3.19 (1H, dd, J = 12.5 & 6.6 Hz), 3.39 (3H, s), 3.40 (1H, m), 3.60 - 4.10 (11H, m), 4.23 (4H, m).

# Example 47

UV<sub>max</sub> nm (H<sub>2</sub>O): 297;  
 IR<sub>max</sub> cm<sup>-1</sup> (KBr): 3400 (br), 1742, 1624, 1590, 1382;  
 NMR  $\delta$  (D<sub>2</sub>O): 1.24 (3H, d, J = 7.3 Hz), 1.31 (3H, d, J = 6.3 Hz), 1.85 (1H, m), 2.92 (1H, m), 3.28 (1H, m), 3.47 (5H, m), 3.80 - 4.37 (15H, m), 4.52 (1H, m).

## Reference Example 1

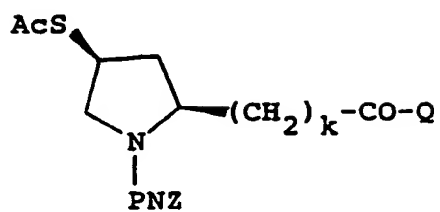


To a solution of cis-1-(p-nitrobenzyloxycarbonyl)-4-acetylthio-L-proline (552 mg; 1.5 mmol) and triethylamine (303 mg; 3.0 mmol) in dry tetrahydrofuran (6 ml), a solution of ethyl chloroformate (184 mg; 1.7 mmol) in dry tetrahydrofuran (1.5 ml) was dropwise added under ice-cooling, followed by stirring for 0.5 hour. To the reaction mixture, 4-(3-aminopropyl)pyridine (306 mg; 2.25 mmol) was added, and the resultant mixture was stirred for 1 hour. The reaction mixture was diluted with ethyl acetate, washed with aqueous sodium hydrogen carbonate solution and aqueous sodium chloride solution in order and dried over anhydrous magnesium sulfate-anhydrous sodium carbonate. After removal of the solvent, the residue was purified by silica gel chromatography to give (2S,4S)-1-(p-nitrobenzyloxycarbonyl)-2-[3-(4-pyridyl)propyl]-aminocarbonyl-4-acetylthiopyrrolidine.

IR<sub>max</sub> cm<sup>-1</sup> (neat): 3300 (br), 1693, 1602, 1520, 1400, 1340, 1107;  
 NMR  $\delta$  (CDCl<sub>3</sub>): 2.32 (3H, s), 2.4 - 2.8 (4H, m), 3.2 - 3.5 (3H, m), 3.9 - 4.1 (1H, m), 4.1 - 4.2 (1H, m), 4.3 - 4.4 (1H, m), 5.25 (2H, s), 6.66 (1H, br.s), 7.10 (2H, d, J = 5.0 Hz), 7.49 (2H, d, J = 7.6 Hz), 8.20 (2H, d, J = 8.3 Hz), 8.49 (2H, m).

## Reference Examples 2 to 16

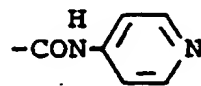
In the same manner as in Reference Example 1, the thioacetates as shown in Table 6 were obtained from the corresponding amines. The physical properties of the compounds obtained follow the Table.

Table 6

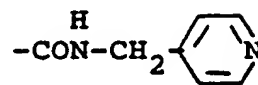
Reference  
Example No.

(CH<sub>2</sub>)<sub>k</sub>-CO-Q

2



3



	Refer nc Example No.	$(\text{CH}_2)_k\text{-CO-Q}$
5	4	$\text{-CON-}\overset{\text{H}}{\text{C}}\text{-}\text{C}_5\text{H}_4\text{N}$
10	5	$\text{-CON-CH}_2\text{-}\text{C}_5\text{H}_4\text{N}$
15	6	$\text{-CON-}(\text{CH}_2)_2\text{-}\text{C}_5\text{H}_4\text{N}$
20	7	$\text{-CON-}(\text{CH}_2)_3\text{-}\text{C}_5\text{H}_4\text{N}$
25	8	$\text{-CON-}(\text{CH}_2)_4\text{-}\text{C}_5\text{H}_4\text{N}$
30	9	$\text{-CON-}\begin{cases} (\text{CH}_2)_2\text{-OH} \\ \text{CH}_2\text{-}\text{C}_5\text{H}_4\text{N} \end{cases}$
35	10	$\text{-CON-CH}_2\text{-}\text{C}_5\text{H}_4\text{N}$
40	11	$\text{-CON-}(\text{CH}_2)_2\text{-}\text{C}_5\text{H}_4\text{N}$
45	12	$\text{-CON-}\overset{\text{Me}}{\text{C}}\text{-}(\text{CH}_2)_2\text{-}\text{C}_5\text{H}_4\text{N}$
50	13	$\text{-CON-}(\text{CH}_2)_2\text{-}\text{C}_5\text{H}_3\text{NMe}$
55	14	$\text{-CON-}(\text{CH}_2)_2\text{-}\text{C}_5\text{H}_3\text{NMe}$
	15	$\text{-CON-CH}_2\text{-}\text{C}_5\text{H}_8\text{NMe}$



Reference Example 9

5 IR<sub>max</sub> cm<sup>-1</sup> (CHCl<sub>3</sub>): 3400 (br), 1690, 1685 (sh), 1655, 1521, 1422, 1345, 1200, 1120;  
 NMR δ (CDCl<sub>3</sub>): 2.35 (3H, s), 3.2 - 3.6 (3H, m), 3.6 - 4.8 (8H, m), 4.8 - 5.2 (2H, m), 5.24 (2H, s),  
 7.2 - 7.5 (1H, m), 7.51 (2H, d, J = 8.9 Hz), 7.6 - 7.8 (1H, m), 8.23 (2H, d, J =  
 8.9 Hz), 8.4 - 8.7 (2H, m).

Reference Example 10

10 IR<sub>max</sub> cm<sup>-1</sup> (KBr): 3310, 1767, 1700, 1653, 1518, 1435, 1344, 1260, 1240, 1172, 1098;  
 NMR δ (CDCl<sub>3</sub>): 2.28 (1H, m), 2.30 (3H, s), 2.75 (1H, m), 3.44 (1H, m), 3.99 (1H, m), 4.21 (1H, m),  
 4.53 (3H, m), 5.12 (1H, m), 5.24 (2H, br. s), 7.2 - 7.7 (5H, m), 8.0 (1H, m), 8.23  
 (1H, m), 8.51 (1H, m).

Reference Example 11

15 NMR δ (CDCl<sub>3</sub>): 2.20 (1H, m), 2.28 (3H, s), 2.98 (2H, m), 3.37 (1H, m), 3.64 (2H, m), 4.03 (1H, m),  
 5.23 (2H, m), 7.3 - 7.7 (4H, m), 8.03 (2H, m), 8.19 (1H, m), 8.42 (1H, m).

Reference Example 12

20 IR<sub>max</sub> cm<sup>-1</sup> (neat): 3400, 1684, 1653, 1421, 1396, 1337, 1104;  
 NMR δ (CDCl<sub>3</sub>): 1.82 (1H, m), 2.3 - 2.4 (3H, m), 2.5 - 3.25 (3H, m), 2.9 - 3.0 (3H, m), 3.45 (2H, m),  
 3.5 - 4.1 (5H, m), 4.13 (2H, m), 4.73 (1H, m), 5.23 (2H, m), 7.1 - 7.7 (4H, m), 8.20  
 (2H, m), 8.52 (1H, m).

Reference Example 13

30 IR<sub>max</sub> cm<sup>-1</sup> (neat): 3300, 1675, 1595, 1510, 1415, 1392, 1333, 1284, 1247, 1198, 1160, 1103;  
 NMR δ (CDCl<sub>3</sub>): 2.33 (3H, s), 2.35 (1H, m), 2.51 (3H, s), 2.78 (2H, m), 3.34 (1H, dd, J = 11.2 &  
 6.3 Hz), 3.50 (2H, m), 3.95 (1H, m), 4.10 (1H, dd, J = 8.6 & 6.9 Hz), 4.31 (1H, dd,  
 J = 8.6 & 5.6 Hz), 5.17 (1H, d, J = 13.5 Hz), 5.24 (1H, d, J = 13.5 Hz), 6.72  
 (1H, br. s), 7.09 (1H, d, J = 7.9 Hz), 7.3 - 7.7 (3H, m), 8.22 (2H, d, J = 8.2 Hz),  
 8.31 (1H, s).

Reference Example 14

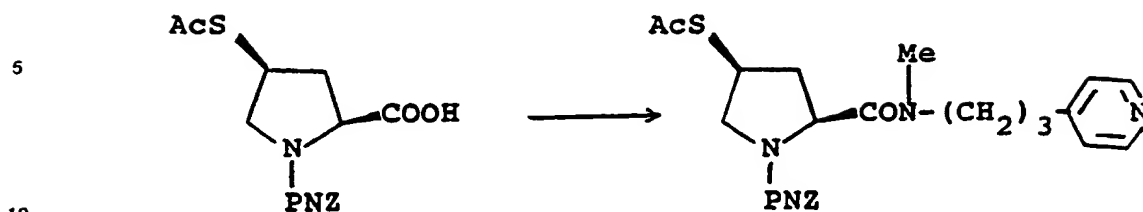
40 IR<sub>max</sub> cm<sup>-1</sup> (KBr): 3320, 1705, 1656, 1518, 1399, 1340, 1160, 1115;  
 NMR δ (CDCl<sub>3</sub>): 1.65 (1H, m), 2.33 (3H, s), 2.50 (1H, s), 2.57 (3H, s), 2.83 (2H, m), 3.34 (1H, dd, J  
 = 10.8 & 5.9 Hz), 3.50 (2H, m), 3.97 (1H, m), 4.10 (1H, dd, J = 11.2 & 6.9 Hz),  
 4.34 (1H, dd, J = 7.9 & 6.3 Hz), 5.20 (2H, m), 7.06 (1H, dd, J = 3.9 & 7.6 Hz),  
 7.42 (1H, m), 7.50 (2H, m), 8.22 (2H, d, J = 8.6 Hz), 8.37 (1H, d, J = 3.9 Hz).

Reference Example 15

45 IR<sub>max</sub> cm<sup>-1</sup> (KBr): 3320, 1700, 1665, 1605, 1550, 1518, 1428, 1402, 1342, 1178, 1118;  
 NMR δ (CDCl<sub>3</sub>): 1.15 - 1.95 (7H, m), 2.24 (3H, s), 2.33 (3H, s), 2.4-2.7 (1H, m), 2.7 - 3.0 (2H, m),  
 3.0 - 3.3 (2H, m), 3.3 - 3.5 (1H, m), 3.9 - 4.5 (4H, m), 5.24 (2H, s), 6.65 (1H, br. s),  
 7.51 (2H, d, J = 8.4 Hz), 8.23 (2H, d, J = 8.4 Hz).

Reference Example 16

50 IR<sub>max</sub> cm<sup>-1</sup> (KBr): 3290, 1707, 1687, 1645, 1522, 1421, 1340;  
 NMR δ (CDCl<sub>3</sub>): 1.1 - 1.8 (5H, m), 1.8 - 2.0 (5H, m), 2.24 (3H, s), 2.33 (3H, s), 2.4 - 2.6 (1H, m),  
 2.82 (2H, d, J = 11.0 Hz), 3.2 - 3.6 (3H, m), 3.9 - 4.25 (2H, m), 4.3 - 4.5 (1H, m),  
 5.26 (2H, s), 6.51 (1H, br. s), 7.51 (2H, d, J = 8.3 Hz), 8.24 (2H, d, J = 8.3 Hz).

Reference Example 17

To a solution of cis-1-(p-nitrobenzyloxycarbonyl)-4-acetylthio-L-proline (736 mg; 2.0 mmol) in dry methylene chloride (6 ml), a catalytic amount of dimethylformamide was added, and a solution of oxalic chloride (305 mg; 2.4 mmol) in dry methylene chloride (2 ml) was added thereto. The resultant mixture was stirred at room temperature for 1 hour. Under ice-cooling, methyl [3-(4-pyridyl)propyl]amine (300 mg; 2.0 mmol) and a solution of triethylamine (485 mg; 4.8 mmol) in dry methylene chloride (2. ml) were added thereto, followed by stirring for 15 minutes. The reaction mixture was combined with aqueous sodium hydrogen carbonate solution, and the organic phase was separated from the aqueous phase, washed with aqueous sodium chloride solution and dried over anhydrous magnesium sulfate. After removal of the solvent, the residue was purified by silica gel column chromatography to give (2S,4s)-1-(p-nitrobenzyloxycarbonyl)-2-[3-(4-pyridyl)propyl]methylaminocarbonyl-4-acetylthiopyrrolidine.

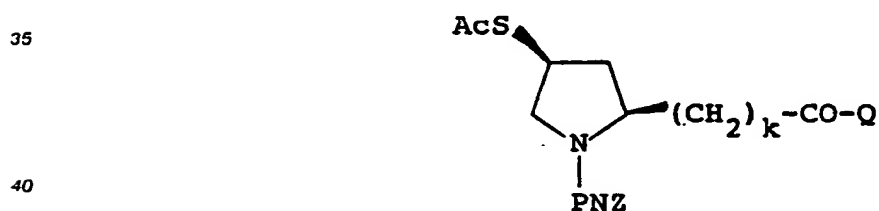
IR<sub>max</sub> cm<sup>-1</sup> (neat): 1715 (sh), 1700, 1654, 1600, 1518, 1340, 1160, 1107;  
 NMR δ (CDCl<sub>3</sub>): 1.7 - 2.2 (3H, m), 2.33 (3H, s), 2.4 - 2.9 (3H, m), 2.9 - 3.1 (3H, m), 3.3 - 3.7 (3H, m), 3.9 - 4.2 (2H, m), 4.5 - 4.8 (1H, m), 5.21 (2H, s), 6.9 - 7.2 (2H, m), 7.3 - 7.6 (2H, m), 8.1 - 8.3 (2H, m), 8.4 - 8.6 (2H, m).

25

Reference Examples 18 to 26

In the same manner as in Reference Example 17, the thioacetates as shown in Table 7 were obtained from the corresponding amines. The physical properties of the compounds obtained follow the Table.

30

Table 7

45

50

55

	Refer nce Example No.	$(CH_2)_k-CO-O$
5	18	$\begin{array}{c} \text{Me} \\   \\ -\text{CON}-(CH_2)_2-\text{C}_5\text{H}_4\text{N} \end{array}$
10	19	$\begin{array}{c} \text{Me} \\   \\ -\text{CON}-(CH_2)_2-\text{C}_5\text{H}_4\text{N} \end{array}$
15	20	$\begin{array}{c} \text{Me} \\   \\ -\text{CON}-(CH_2)_3-\text{C}_5\text{H}_4\text{N} \end{array}$
20	21	$\begin{array}{c} \text{Me} \\   \\ -\text{CON}-(CH_2)_4-\text{C}_5\text{H}_4\text{N} \end{array}$
25	22	$\begin{array}{c} \text{Me} \\   \\ -\text{CON}-(CH_2)_3-\text{C}_5\text{H}_4\text{N} \end{array}$
30	23	$-\text{CON}-\text{C}_6\text{H}_{11}-\text{CH}_2\text{CH}_2-\text{N}(\text{Me})_2$
35	24	$-\text{CON}-\text{C}_6\text{H}_{11}-\text{N}(\text{CH}_2)_2-\text{O}-\text{TBDMS}$
40	25	$-\text{CON}-\text{C}_6\text{H}_{11}-\text{N}(\text{CH}_2)_3-\text{OH}$
45	26	$-\text{CON}-\text{C}_6\text{H}_{11}-\text{N}(\text{CH}_2)_2-\text{O}-\text{Me}$

Physical properties50 Reference Example 18IR<sub>max</sub> cm<sup>-1</sup> (neat):NMR δ (CDCl<sub>3</sub>):

1715 (sh), 1700, 1687 (sh), 1602, 1520, 1340, 1162, 1107;

1.7 - 2.0 (1H, m), 2.34 (3H, s), 2.5 - 3.1 (6H, m), 3.3 - 3.85 (3H, m), 3.85 - 4.2 (2H, m), 4.5 - 4.8 (1H, m), 5.22 (2H, s), 7.0 - 7.25 (2H, m), 7.4 - 7.6 (2H, m), 8.1 - 8.3 (2H, m), 8.45 - 8.65 (2H, m).

55

Reference Example 19

# EP 0 442 497 A1

IR<sub>max</sub> cm<sup>-1</sup> (n at): 1730 (sh), 1692 (sh), 1660, 1507, 1390, 1335, 1150, 1110;  
 NMR δ (CDCl<sub>3</sub>): 1.6 - 1.9 (1H, m), 2.34 (3H, s), 2.5 - 3.1 (6H, m), 3.3 - 4.3 (5H, m), 4.5 - 4.8 (1H, m), 5.22 (2H, s), 7.2 - 7.4 (1H, m), 7.4 - 7.7 (3H, m), 8.22 (2H, d, J = 8.9 Hz), 8.47 (2H, br. s).

5

## Reference Example 20

IR<sub>max</sub> cm<sup>-1</sup> (neat): 2930, 1715 (sh), 1704, 1696 (sh), 1650, 1518, 1420, 1400, 1340, 1105;  
 NMR δ (CDCl<sub>3</sub>): 1.7 - 2.2 (3H, m), 2.33 (3H, s), 2.4 - 2.85 (3H, m), 2.85 - 3.15 (3H, m), 3.3 - 3.6 (2H, m), 3.85 - 4.2 (2H, m), 4.45 - 4.8 (1H, m), 5.22 (2H, s), 7.1 - 7.3 (1H, m), 7.3 - 7.6 (3H, m), 8.05 - 8.3 (2H, m), 8.3 - 8.6 (2H, m).

10

## Reference Example 21

IR<sub>max</sub> cm<sup>-1</sup> (neat): 2925, 1714 (sh), 1682, 1654, 1518, 1420, 1400, 1340, 1160, 1115;  
 NMR δ (CDCl<sub>3</sub>): 1.8 - 2.15 (2H, m), 2.33 (3H, s), 2.4 - 2.8 (3H, m), 2.8 - 3.1 (3H, m), 3.2 - 3.6 (3H, m), 3.9 - 4.2 (3H, m), 4.69 (1H, m), 5.20 (2H, m), 7.1 - 7.6 (4H, m), 8.1 - 8.3 (2H, m), 8.3 - 8.6 (2H, m).

15

## Reference Example 22

IR<sub>max</sub> cm<sup>-1</sup> (neat): 1720 (sh), 1705, 1650, 1515, 1430, 1400, 1340, 1110;  
 NMR δ (CDCl<sub>3</sub>): 1.7 - 2.3 (2H, m), 2.33 (3H, s), 2.5 - 3.2 (7H, m), 3.2 - 3.7 (3H, m), 3.8 - 4.3 (2H, m), 5.6 - 5.8 (1H, m), 5.21 (2H, s), 7.0 - 7.3 (2H, m), 7.4 - 7.7 (3H, m), 8.0 - 8.3 (2H, m), 8.5 - 8.7 (1H, m).

25

## Reference Example 23

IR<sub>max</sub> cm<sup>-1</sup> (neat): 2920, 1700 (sh), 1688, 1642, 1507, 1400, 1336, 1100;  
 NMR δ (CDCl<sub>3</sub>): 0.8 - 2.0 (10H, m), 2.21 (6H, s), 2.33 (3H, s), 2.5 - 3.2 (3H, m), 3.3 - 5.0 (5H, m), 5.22 (2H, s), 7.51 (2H, d, J = 8.5 Hz), 8.22 (2H, d, J = 8.5 Hz).

30

## Reference Example 24

IR<sub>max</sub> cm<sup>-1</sup> (neat): 1700, 1660, 1523, 1438, 1402, 1342, 1253, 1103;  
 NMR δ (CDCl<sub>3</sub>): 0.05 (6H, s), 0.89 (9H, s), 1.88 (1H, m), 2.33 (3H, s), 2.50 (6H, m), 3.40 (2H, m), 3.55 (2H, m), 3.72 (1H, m), 3.75 (2H, m), 4.00 (1H, m), 4.13 (2H, m), 4.72 (1H, m), 5.05 - 5.40 (2H, m), 7.50 (2H, m), 8.23 (2H, m).

35

## Reference Example 25

IR<sub>max</sub> cm<sup>-1</sup> (neat): 3450 (br), 1700, 1653, 1521, 1435, 1342, 1120;  
 NMR δ (CDCl<sub>3</sub>): 1.80 - 2.00 (1H, m), 2.2 - 2.9 (8H, m), 2.34 (3H, s), 3.3 - 3.9 (8H, m), 3.9 - 4.2 (2H, m), 4.6 - 4.8 (1H, m), 5.0 - 5.4 (2H, m), 7.51 (2H, d, J = 8.9 Hz), 8.22 (2H, d, J = 8.9 Hz).

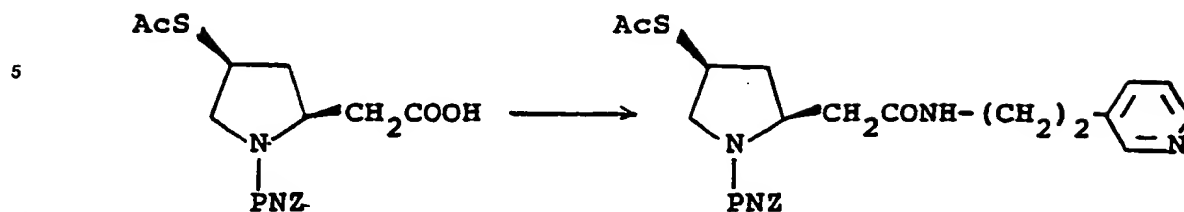
45

## Reference Example 26

NMR δ (CDCl<sub>3</sub>): 1.90 (1H, m), 2.34 (3H, s), 2.30 - 2.85 (7H, m), 3.34 (3H x 0.3, s), 3.35 (3H x 0.7, s), 3.40 - 3.78 (7H, m), 4.01 (1H, m), 4.14 (1H, m), 4.75 (1H, m), 5.07 (0.3H, d, J = 13.9 Hz), 5.23 (2H x 0.7, s), 5.31 (0.3H, d, J = 13.9 Hz), 7.50 (2H, m), 8.23 (2H, m).

50

55

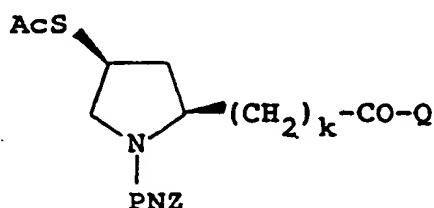
Reference Example 27

In the same manner as in Reference Example 1, there was obtained (2R,4S)-1-(p-nitrobenzyloxycarbonyl)-2-[2-(3-pyridylethyl)aminocarbonyl]methyl-4-acetylthiopyrrolidine from (2R,4S)-1-(p-nitrobenzyloxycarbonyl)-2-carboxymethyl-4-acetylthiopyrrolidine (382 mg; 1.0 mmol).

15 IR<sub>max</sub> cm<sup>-1</sup> (neat): 3295 (br), 1690 (sh), 1680, 1650 (sh), 1513, 1418, 1395, 1338, 1100;  
 NMR δ (CDCl<sub>3</sub>): 2.2 - 2.7 (2H, m), 2.34 (3H, s), 2.7 - 3.0 (3H, m), 3.25 (1H, dd, J = 7.3 & 11.2 Hz), 3.4 - 3.7 (2H, m), 3.8 - 4.3 (3H, m), 5.19 (2H, s), 5.98 (1H, br.s), 7.15 - 7.35 (1H, m), 7.35 - 7.65 (3H, m), 8.22 (2H, d, J = 8.6 Hz), 8.4 - 8.6 (2H, m).

20 Reference Examples 28 and 29

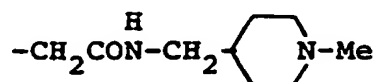
In the same manner as in Reference Example 27, the thioacetates as shown in Table 8 were obtained from the corresponding amines. The physical properties of the compounds obtained follow the Table.

25 Table 8

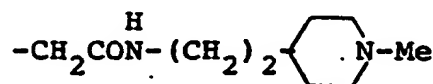
40 Reference  
Example No.

(CH<sub>2</sub>)<sub>k</sub>-CO-Q

28



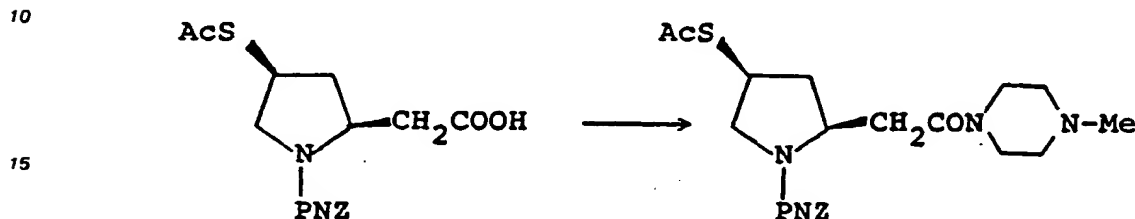
29

50 Physical propertiesReference Example 28

55 IR<sub>max</sub> cm<sup>-1</sup> (KBr): 3310, 1700, 1645, 1527, 1445, 1430, 1405, 1347, 1320, 1200, 1147, 1110;  
 NMR δ (CDCl<sub>3</sub>): 1.15 - 1.55 (4H, m), 1.55 - 2.0 (5H, m), 2.25 (3H, s), 2.34 (3H, s), 2.4 - 2.7 (1H, m), 2.7 - 3.0 (3H, m), 3.0 - 3.6 (3H, m), 3.8 - 4.5 (3H, m), 5.21 (2H, s), 5.86 (1H, br. s), 7.52 (2H, d, J = 8.8 Hz), 8.23 (2H, d, J = 8.8 Hz).

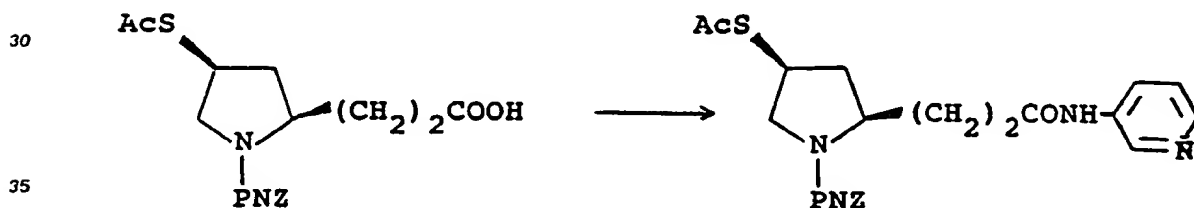
Reference Example 29

IR<sub>max</sub> cm<sup>-1</sup> (KBr): 3290, 1690 (sh), 1687, 1630, 1520, 1424, 1342;  
 NMR δ (CDCl<sub>3</sub>): 1.1 - 1.5 (5H, m), 1.5 - 1.8 (3H, m), 1.87 (2H, t, J = 10.7 Hz), 2.25 (3H, s), 2.34 (3H, s), 2.4 - 2.7 (2H, m), 2.7 - 3.0 (3H, m), 3.1 - 3.4 (3H, m), 3.8 - 4.3 (3H, m), 5.21 (2H, s), 5.71 (1H, br. s), 7.51 (2H, d, J = 8.6 Hz), 8.23 (2H, d, J = 8.6 Hz).

Reference Example 30

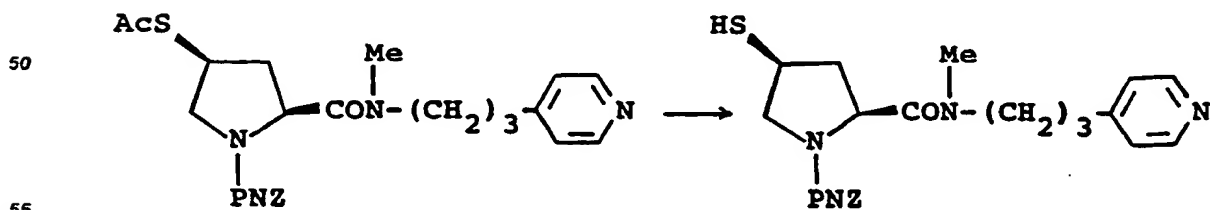
In the same manner as in Reference Example 2, there was obtained (2R,4S)-1-(p-nitrobenzyloxycarbonyl)-2-[(4-methyl)piperazin-1-yl]carbonylmethyl-4-acetylthiopyrrolidine from (2R,4S)-1-(p-nitrobenzyloxycarbonyl)-2-carboxymethyl-4-acetylthiopyrrolidine (382 mg; 1.0 mmol).

IR<sub>max</sub> cm<sup>-1</sup> (neat) : 1687, 1634, 1515, 1420, 1398, 1340, 1285, 1100;  
 NMR δ (CDCl<sub>3</sub>): 1.8 - 2.0 (1H, m), 2.2 - 2.6 (6H, m), 2.29 (3H, s), 2.34 (3H, s), 2.6 - 2.9 (1H, m), 3.2 - 3.8 (5H, m), 3.8 - 4.0 (1H, m), 4.0 - 4.5 (2H, m), 5.21 (2H, s), 7.51 (2H, d, J = 8.6 Hz), 8.23 (2H, d, J = 8.6 Hz).

Reference Example 31

In the same manner as in Reference Example 2, there was obtained (2R,4S)-1-(p-nitrobenzyloxycarbonyl)-2-[(3-pyridylamino)carbonyl]ethyl-4-acetylthiopyrrolidine from (2R,4S)-1-(p-nitrobenzyloxycarbonyl)-2-(2-carboxyethyl)-4-acetylthiopyrrolidine (198 mg; 0.50 mmol).

IR<sub>max</sub> cm<sup>-1</sup> (neat): 3280 (br), 1700 (sh), 1680, 1516, 1400, 1338;  
 NMR δ (CDCl<sub>3</sub>): 1.6 - 2.8 (6H, m), 2.35 (3H, s), 3.28 (1H, dd, J = 6.8 & 11.7 Hz), 3.92 (1H, m), 4.0 - 4.3 (2H, m), 5.26 (2H, s), 7.2 - 7.4 (2H, m), 7.53 (2H, d, J = 8.7 Hz), 8.25 (2H, d, J = 8.7 Hz), 8.3 - 8.45 (1H, m), 8.67 (1H, d, J = 2.3 Hz), 9.23 (1H, br. s).

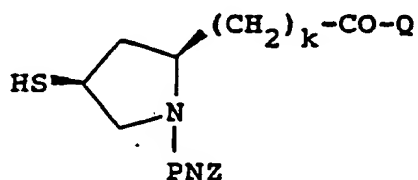
Reference Example 32













To a solution of (2S,4S)-1-(p-nitrobenzyloxycarbonyl)-2-[(3-(4-pyridyl)propyl)methylaminocarbonyl]-4-acetylthiopyrrolidine (332 mg) in methanol (30 ml), 1N aqueous sodium hydroxide solution (0.70 ml) was

added at room temperatur , and the resultant mixtur was stirred for 10 minutes. 1N Hydrochloric acid (0.70 ml) was added to the reaction mixture, and m thanol was removed by distillation under reduced pressure. The residue was combined with dichloromethane, washed with water and dried over anhydrous magnesium sulfate, followed by removal of th solvent to give (2S,4S)-1-p-nitrobenzyloxycarbonyl-2-(3-(4-pyridyl)-propyl)methylaminocarbonyl-4-mercaptopyrrolidine, which was subjected to the subsequent reaction without purification.

In the same manner as in Reference Example 32, the mercaptan compounds as shown in Table 9 were obtained from the corresponding thioacetates.

Table 9



	<u>No.</u>	<u>k</u>	<u>Q</u>
5	1	0	$\text{H}$ $-\text{N}-\text{CH}_2-$ 
10	2	0	$\text{H}$ $-\text{N}-(\text{CH}_2)_2-$ 
15	3	0	$\text{Me}$ $ \text{N}-(\text{CH}_2)_2-$ 
20	4	0	$\text{Me}$ $ \text{N}-(\text{CH}_2)_3-$ 
25	5	0	$\text{H}$ $-\text{N}-$ 
30	6	0	$\text{H}$ $-\text{N}-\text{CH}_2-$ 
35	7	0	$\text{H}$ $-\text{N}-(\text{CH}_2)_2-$ 
40	8	0	$\text{H}$ $-\text{N}-(\text{CH}_2)_3-$ 
45	9	0	$\text{H}$ $-\text{N}-(\text{CH}_2)_4-$ 
50	10	0	$\text{Me}$ $ \text{N}-(\text{CH}_2)_2-$ 
55	11	0	$\text{Me}$ $ \text{N}-(\text{CH}_2)_3-$ 
	12	0	$\text{Me}$ $ \text{N}-(\text{CH}_2)_4-$ 

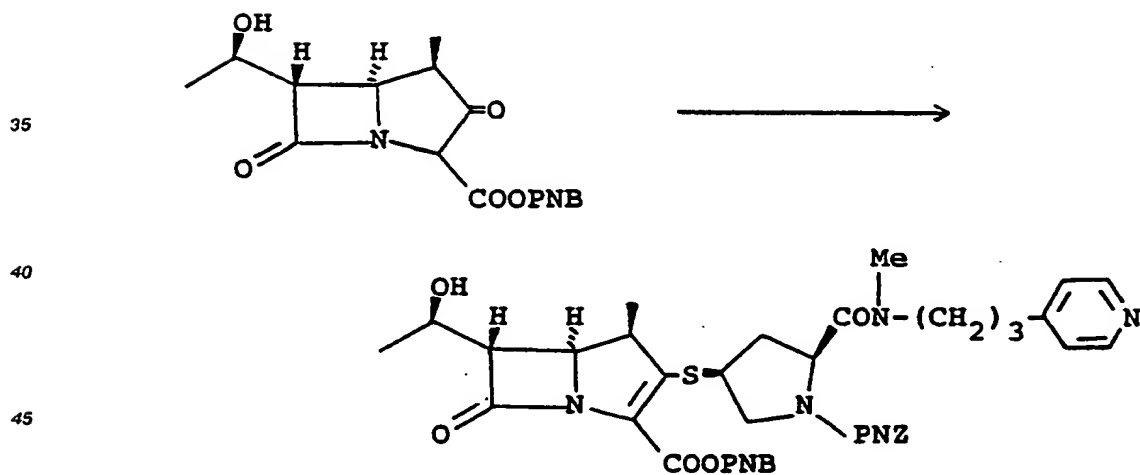


	<u>No.</u>	<u>k</u>	<u>Q</u>
5	13	0	
	14	0	
10	15	0	
15	16	0	
20	17	0	
25	18	0	
30	19	0	
35	20	1	
	21	2	
40	22	0	
	23	1	
45	24	0	
50	25	1	

55

	<u>No.</u>	<u>k</u>	<u>Q</u>
5	26	0	
10	27	0	
15	28	0	
20	29	1	
	30	0	
25	31	0	

## Reference Example 33



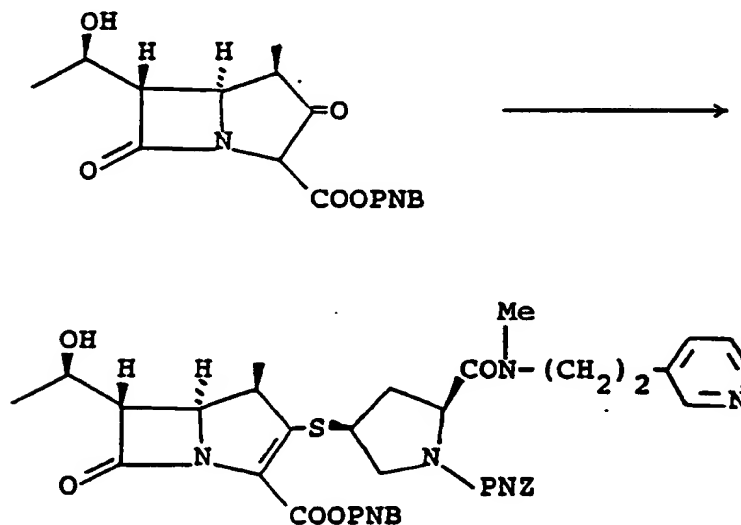
To a solution of (4R,5R,6S,8R)-p-nitrobenzyl-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-3,7-dione-2-carboxylate (218 mg) in dry acetonitrile (2.0 ml), diisopropylethylamine (94 mg) and diphenyl chlorophosphate (178 mg) were added under ice-cooling, and the resultant mixture was stirred at the same temperature for 2 hours. A solution of (2S,4S)-p-nitrobenzyloxycarbonyl-2-((3-(4-pyridyl)propyl)-methylaminocarbonyl-4-mercaptopyrrolidine (311 mg) and diisopropylethylamine (94 mg) in dry acetonitrile (3.0 ml) was added to the reaction mixture, followed by stirring for 2 hours. The reaction mixture was diluted with ethyl acetate, washed with aqueous potassium phosphate solution and a saturated aqueous sodium chloride solution in order and dried over anhydrous magnesium sulfate. After removal of the solvent, the residue was purified by silica gel column chromatography to give (4R,5S,6S,8R,2'S,4'S)-p-nitrobenzyl-3-[1-p-nitrobenzyloxycarbonyl-2-((3-(4-pyridyl)propyl)methylaminocarbonyl)pyrrolidin-4-ylthio]-4-methyl-6-(1-

hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-en-7-one-2-carboxylate.

IR<sub>max</sub> cm<sup>-1</sup> (neat): 3380, 1763, 1700, 1644, 1601, 1517, 1403, 1339;

NMR δ (CDCl<sub>3</sub>): 1.28 (3H, d, J = 6.9 Hz), 1.37 (3H, d, J = 6.3 Hz), 3.08, 2.96 (3H as a whole, each s), 5.21 (2H, br.s), 5.24 (1H, d, J = 13.8 Hz), 5.51 (1H, d, J = 13.8 Hz), 6.97 - 7.20 (2H, m), 7.35 - 7.63 (2H, m), 7.65 (2H, d, J = 8.9 Hz), 8.10 - 8.30 (4H, m), 8.52 (2H, m).

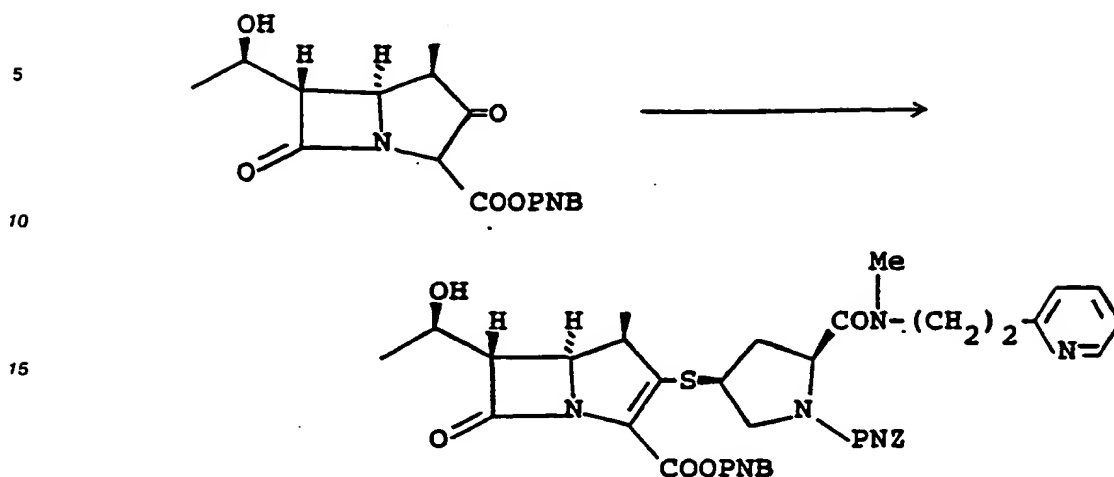
### Reference Example 34



To a solution of (4R,5R,6S,8R)-p-nitrobenzyl-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-3,7-dione-2-carboxylate (54 mg) in dry acetonitrile (1.0 ml), diisopropylethylamine (22 mg) and diphenyl chlorophosphate (45 mg) were added under ice-cooling, and the resultant mixture was stirred at the same temperature for 1 hour. A solution of (2S,4S)-1-p-nitrobenzyloxycarbonyl-2-((2-(3-pyridyl)ethyl)-methylaminocarbonyl)-4-mercaptopyrrolidine (95 mg) and diisopropylethylamine (22 mg) in dry acetonitrile (1.0 ml) was added to the reaction mixture, followed by stirring for 1.5 hours. The reaction mixture was diluted with dichloromethane, washed with water and dried over anhydrous magnesium sulfate. After removal of the solvent, the residue was purified by silica gel column chromatography to give (4R,5S,6S,8R,2'S,4'S)-p-nitrobenzyl-3-[1-p-nitrobenzyloxycarbonyl-2-((2-(3-pyridyl)ethyl)-methylaminocarbonyl)pyrrolidin-4-ylthio]-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-en-7-one-2-carboxylate.

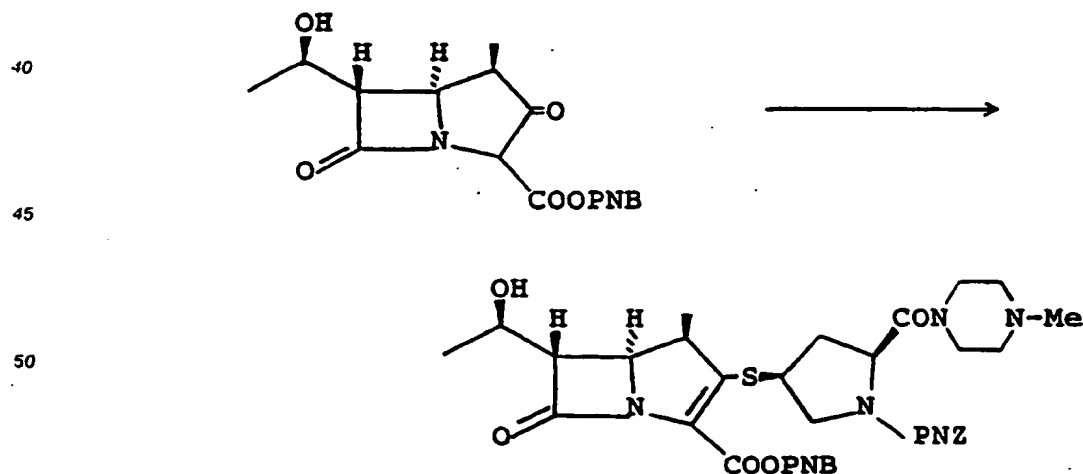
IR<sub>max</sub> cm<sup>-1</sup> (neat): 3400, 1755, 1690, 1512, 1332;

NMR δ (CDCl<sub>3</sub>): 1.27 (3H, d, J = 7.0 Hz), 1.37 (3H, d, J = 6.3 Hz), 2.88, 2.96, 3.00 (3H as a whole, each s), 3.27 (1H, m), 5.30 (3H, m), 5.50 (1H, d, J = 13.5 Hz), 7.26 (1H, m), 7.4 - 7.6 (3H, m), 7.65 (2H, d, J = 8.6 Hz), 8.22 (4H, d, J = 8.6 Hz), 8.4 - 8.6 (2H, m).

Reference Example 35

To a solution of (4R,5R,6S,8R)-p-nitrobenzyl-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-3,7-dione-2-carboxylate (181 mg) in dry acetonitrile (2.0 ml), diisopropylethylamine (81 mg) and diphenyl chlorophosphate (175 mg) were added under ice-cooling, and the resultant mixture was stirred at the same temperature for 1 hour. A solution of (2S,4S)-p-nitrobenzyloxycarbonyl-2-((2-(2-pyridyl)ethyl)-methylaminocarbonyl-4-mercaptopyrrolidine (303 mg) in dry acetonitrile (3.0 ml) and then diisopropylethylamine (81 mg) were added to the reaction mixture, followed by stirring for 2 hours. The reaction mixture was diluted with ethyl acetate, washed with aqueous potassium phosphate solution and a saturated aqueous sodium chloride solution in order and dried over magnesium sulfate. After removal of the solvent, the residue was purified by silica gel column chromatography to give (4R,5S,6S,8R,2'S,4'S)-p-nitrobenzyl-3-[1-p-nitrobenzyloxycarbonyl-2-((2-(2-pyridyl)ethyl)methylaminocarbonyl)pyrrolidin-4-ylthio]-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-en-7-one-2-carboxylate.

NMR  $\delta$  (CDCl<sub>3</sub>): 1.28 (3H, d, J = 7.3 Hz), 1.34 (3H, d, J = 6.3 Hz), 1.87 (1H, m), 2.73 (1H, m), 2.92, 2.93, 2.95, 3.01 (3H as a whole, each s), 4.80 (1H, m), 5.26 (3H, m), 5.49 (1H, d, J = 13.9 Hz), 7.00 - 7.75 (7H, m), 8.22 (4H, m), 8.50 (1H, m).

Reference Example 36

To a solution of (4R,5R,6S,8R)-1-p-nitrobenzyl-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-3,7-dione-2-carboxylate (2.55 g) in dry acetonitrile (10.0 ml), diisopropylethylamine (1.09 g) and diphenyl chlorophosphate (2.06 g) were added under ice-cooling, and the resultant mixture was stirred at the same

temperature for 2 hours. A solution of (2S,4S)-p-nitrobenzyloxycarbonyl-2-(4-methylpiperazin-1-ylcarbonyl)-4-mercaptopyrrolidine (3.08 g) and diisopropylethylamin (1.09 g) in dry acetonitrile (10.0 ml) was added to the reaction mixture, followed by stirring for 4 hours. The reaction mixture was diluted with ethyl acetate, washed with aqueous potassium phosphate solution and a saturated aqueous sodium chloride solution in order and dried over anhydrous magnesium sulfate. After removal of the solvent, the residue was purified by silica gel column chromatography to give (4R,5S,6S,8R,2'S,4'S)-p-nitrobenzyl-3-[1-p-nitrobenzyloxycarbonyl-2-(4-methylpiperazin-1-ylcarbonyl)pyrrolidin-4-ylthio]-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]-hept-2-en-7-one-2-carboxylate.

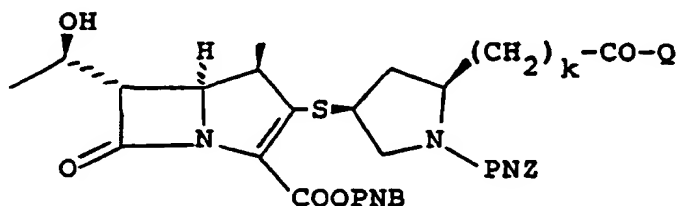
IR<sub>max</sub> cm<sup>-1</sup> (neat): 3400, 1750, 1695, 1630, 1593, 1500, 1423, 1390, 1324, 1271, 1193, 1120;

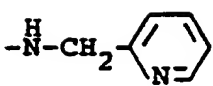
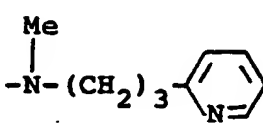
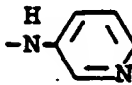
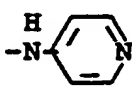
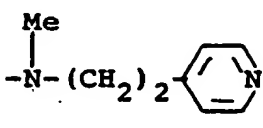
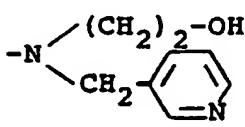
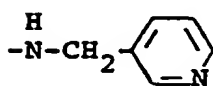
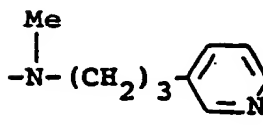
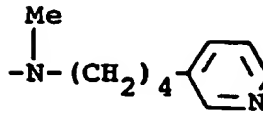
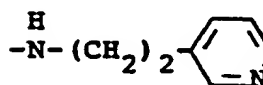
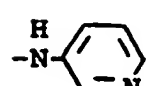
NMR  $\delta$  (CDCl<sub>3</sub>): 1.26 (3H, d, J = 7.3 Hz), 1.34 (3H, d, J = 6.3 Hz), 1.91 (1H, m), 2.32 (3H, s), 2.73 (1H, s), 4.72 (1H, m), 5.22 (3H, m), 5.43 (1H, d, J = 13.9 Hz), 7.40 - 7.60 (2H, m), 7.64 (2H, d, J = 8.9 Hz), 8.20 (4H, d, J = 8.9 Hz).

#### Reference Examples 37 to 50


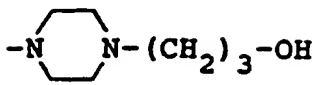
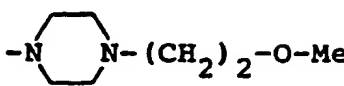
In the same manner as in Reference Example 36, the compounds as shown in Table 10 were obtained. The physical properties of the compounds obtained follow the Table.

**Table 10**



	Reference Example No.	k	Q
5	37	0	
10	38	0	
	39	0	
15	40	0	
20	41	0	
25	42	0	
30	43	0	
35	44	0	
40	45	0	
45	46	1	
50	47	2	

55

	Reference Example No.	k	
5	48	1	
10	49	0	
15	50	0	
20	<u>Physical properties</u>		
25	<u>Reference Example 37</u>		
30	IR <sub>max</sub> cm <sup>-1</sup> (neat): NMR δ (CDCl <sub>3</sub> ):	3370, 1763, 1700, 1602, 1517, 1430, 1398, 1341, 1203, 1130, 1106; 1.27 (3H, d, J = 7.3 Hz), 1.36 (3H, d, J = 6.3 Hz), 2.80 (1H, m), 3.28 (1H, dd, J = 3.0 & 6.9 Hz), 3.36 (1H, m), 3.50 (1H, dd, J = 8.0 & 10.9 Hz), 3.71 (1H, m), 4.30 (2H, m), 5.10 - 5.50 (4H, m), 7.10 - 7.70 (6H, m), 7.98 (1H, m), 8.21 (4H, d, J = 8.9 Hz), 8.39 (1H, m).	
35	<u>Reference Example 38</u>		
40	IR <sub>max</sub> cm <sup>-1</sup> (neat): NMR δ (CDCl <sub>3</sub> ):	3400, 1761, 1697, 1637, 1515, 1426, 1400, 1340, 1202, 1175, 1132, 1104; 1.28 (3H, d, J = 6.9 Hz), 1.34 (3H, d, J = 5.6 Hz), 1.88 (3H, m), 2.50 - 2.90 (4H, m), 2.92, 2.97, 3.00, 3.11 (3H as a whole, each s), 3.28 (1H, m), 3.48 (4H, m), 3.69 (1H, m), 3.87 (1H, m), 4.27 (3H, m), 4.75 (1H, m), 5.23 (3H, m), 5.48 (1H, d, J = 13.9 Hz), 7.39 (1H, dd, J = 4.9 & 8.9 Hz), 7.50 (1H, d, J = 8.9 Hz), 8.06 (1H, t, J = 8.9 Hz), 8.18 (4H, d, J = 8.9 Hz), 8.48 (1H, m).	
45	<u>Reference Example 39</u>		
50	IR <sub>max</sub> cm <sup>-1</sup> (neat): NMR δ (CDCl <sub>3</sub> ):	3330, 1761, 1710, 1603, 1519, 1420, 1340, 1205; 1.26 (3H, d, J = 7.3 Hz), 1.35 (3H, d, J = 6.3 Hz), 3.35 (2H, m), 3.84 (1H, m), 4.03 (1H, m), 4.28 (2H, m), 4.56 (1H, m), 5.17 (1H, d, J = 13.6 Hz), 5.30 (2H, s), 5.33 (1H, d, J = 13.6 Hz), 7.60 (2H, d, J = 8.9 Hz), 8.16 (4H, d, J = 8.9 Hz), 8.35 (1H, m), 8.58 (1H, s).	
55	<u>Reference Example 40</u>		
	IR <sub>max</sub> cm <sup>-1</sup> (neat): NMR δ (CDCl <sub>3</sub> ):	3290, 1760, 1702, 1586, 1508, 1397, 1337, 1203, 1183; 1.27 (3H, d, J = 7.2 Hz), 1.35 (3H, d, J = 6.3 Hz), 2.30 (1H, m), 2.64 (1H, m), 3.32 (2H, m), 3.53 (1H, m), 3.83 (1H, m), 4.00 (1H, m), 4.28 (2H, m), 4.55 (1H, m), 5.18 (1H, d, J = 13.8 Hz), 5.25 (2H, m), 5.38 (1H, d, J = 13.8 Hz), 7.47 (2H, m), 7.60 (2H, d, J = 8.6 Hz), 8.17 (2H, d, J = 8.6 Hz), 8.45 (2H, m).	
	<u>Reference Example 41</u>		
	IR <sub>max</sub> cm <sup>-1</sup> (neat): NMR δ (CDCl <sub>3</sub> ):	3400, 1762, 1698, 1643, 1600, 1517, 1339; 1.27 (3H, d, J = 6.9 Hz), 1.37 (3H, d, J = 6.3 Hz), 2.89, 2.98, 2.98 (3H as a whole, each s), 5.22 (2H, br. s), 5.25 (1H, d, J = 13.9 Hz), 5.49 (1H, d, J = 13.9 Hz), 7.00 - 7.23 (2H, m), 7.40 - 7.58 (2H, m), 7.65 (2H, d, J = 8.6 Hz), 8.21 (4H, m), 8.53 (2H, m).	

Ref erence Example 42

5  $IR_{max}$   $cm^{-1}$  (neat): 3380, 1755, 1693, 1643, 1508, 1337;  
 NMR  $\delta$  ( $CDCl_3$ ): 1.27 (3H, d, J = 7.3 Hz), 1.36 (3H, d, J = 6.3 Hz), 2.03 (1H, m), 2.67 (1H, m), 3.20 - 3.95 (9H, m), 4.05 (1H, m), 4.26 (2H, m), 4.96 (1H, d, J = 13.5 Hz), 5.23 (4H, m), 5.48 (1H, d, J = 13.5 Hz), 7.26 (1H, m), 7.51 (2H, d, J = 8.9 Hz), 7.65 (3H, d, J = 8.6 Hz), 8.22 (4H, m), 8.53 (2H, m).

Reference Example 43

10  $IR_{max}$   $cm^{-1}$  (KBr): 3350, 1774, 1704, 1656, 1600, 1508, 1423, 1395, 1337, 1315;  
 NMR  $\delta$  ( $CDCl_3$ ): 1.24 (3H, m), 1.33 (3H, d, J = 6.3 Hz), 2.47 (1H, m), 2.91 (1H, m), 3.31 (2H, m), 3.54 (1H, dd, J = 5.3 & 11.2 Hz), 3.79 (1H, m), 4.02 (1H, dd, J = 6.0 & 11.2 Hz), 4.20 - 4.60 (5H, m), 5.12 (1H, d, J = 14.2 Hz), 5.20 (2H, br. s), 5.40 (1H, d, J = 14.2 Hz), 7.22 (1H, m), 7.50 (2H, m), 7.60 (2H, d, J = 8.9 Hz), 7.62 (1H, m), 8.13 (4H, d, J = 8.9 Hz), 8.45 (1H, m), 8.50 (1H, s).

Reference Example 44

20  $IR_{max}$   $cm^{-1}$  (KBr): 3410, 1768, 1704, 1653, 1603, 1522, 1422, 1403, 1342, 1262;  
 NMR  $\delta$  ( $CDCl_3$ ): 1.28 (3H, m), 1.37 (3H, d, J = 6.3 Hz), 1.87 (2H, m), 2.70 (3H, m), 2.97, 2.98, 3.09 (3H as a whole, each s), 3.30 - 3.80 (7H, m), 4.78 (2H, m), 5.24 (1H, d, J = 13.8 Hz), 5.30 (2H, br. s), 5.46 (2H, d, J = 13.8 Hz), 7.22 (1H, m), 7.40 (1H, m), 7.50 (2H, d, J = 8.6 Hz), 7.65 (2H, d, J = 8.9 Hz), 8.2 (4H, m), 8.45 (2H, m).

Reference Example 45

25  $IR_{max}$   $cm^{-1}$  (KBr): 3300, 1773, 1707, 1663, 1604, 1518, 1438, 1402, 1340, 1280, 1265, 1206, 1168, 1147, 1109;  
 30 NMR  $\delta$  ( $CDCl_3$ ): 1.27 (3H, m), 1.37 (3H, d, J = 6.3 Hz), 1.80 - 2.10 (4H, m), 2.67 (2H, m), 2.88, 2.93, 2.95, 3.04 (3H as a whole, each s), 5.20 (2H, br.s), 5.25 (1H, d, J = 13.5 Hz), 5.48 (1H, d, J = 13.5 Hz), 7.23 (1H, m), 7.40 (1H, m), 7.51 (2H, d, J = 8.9 Hz), 7.65 (2H, d, J = 8.3 Hz), 8.12 (4H, d, J = 8.9 Hz), 8.42 (2H, m).

Reference Example 46

35  $IR_{max}$   $cm^{-1}$  (neat): 3350, 1760, 1696, 1652, 1517, 1419, 1400, 1338, 1196, 1130, 1102;  
 NMR  $\delta$  ( $CDCl_3$ ): 1.28 (3H, d, J = 7.3 Hz), 1.37 (3H, d, J = 6.0 Hz), 2.82 (2H, m), 5.20 (2H, br. s), 5.23 (1H, d, J = 14.0 Hz), 5.50 (1H, d, J = 14.0 Hz), 7.25 (1H, m), 7.55 (3H, m), 7.66 (2H, d, J = 8.9 Hz), 8.23 (4H, d, J = 8.9 Hz), 8.44 (1H, br.s), 8.48 (1H, d, J = 5.0 Hz).

Reference Example 47

45  $IR_{max}$   $cm^{-1}$  (neat): 3350, 1760, 1700, 1684, 1598, 1518, 1400, 1336;  
 NMR  $\delta$  ( $CDCl_3$ ): 1.27 (3H, d, J = 6.9 Hz), 1.37 (3H, d, J = 6.3 Hz), 2.20 - 2.80 (5H, m), 3.20 - 3.50 (2H, m), 3.28 (1H, dd, J = 2.6 & 6.9 Hz), 3.50 - 3.80 (1H, m), 4.00 - 4.35 (5H, m), 5.37 (2H, ABq, J = 76.9 & 13.9 Hz), 7.53 (2H, d, J = 8.9 Hz), 7.65 (2H, d, J = 8.9 Hz), 8.10 - 8.50 (7H, m), 8.64 (1H, s), 9.09 (1H, br.s).

Reference Example 48

50  $IR_{max}$   $cm^{-1}$  (neat): 3370, 1760, 1695, 1627, 1517, 1433, 1420, 1398, 1337, 1194, 1132, 1101;  
 55 NMR  $\delta$  ( $CDCl_3$ ): 1.28 (3H, d, J = 7.3 Hz), 1.37 (3H, d, J = 6.3 Hz), 2.30 (3H, s), 5.25 (3H, m), 5.50 (1H, d, J = 13.9 Hz), 7.51 (2H, d, J = 8.9 Hz), 7.65 (2H, d, J = 8.9 Hz), 8.22 (4H, m).

Reference Example 49



IR<sub>max</sub> cm<sup>-1</sup> (neat): 3200 (br), 1760, 1700, 1652, 1512, 1336;  
 NMR δ (CDCl<sub>3</sub>): 1.28 (3H, m), 1.36 (3H, d, J = 6.3 Hz), 2.02 (3H, m), 2.73 (1H, m), 3.10 (2H, m),  
 3.24 - 4.80 (18H, m), 5.05 - 5.56 (4H, m), 7.43 (2H x 0.3, d, J = 7.9 Hz), 7.51 (2H  
 x 0.7, d, J = 8.9 Hz), 7.64 (2H, d, J = 8.6 Hz), 8.20 (4H, m).

5

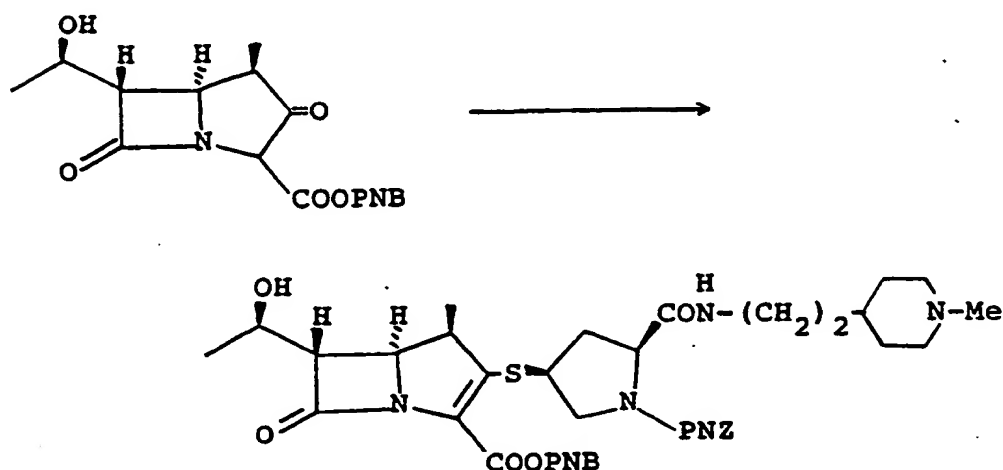
Reference Example 50

IR<sub>max</sub> cm<sup>-1</sup> (neat): 3420 (br), 1763, 1700, 1648, 1602, 1520, 1438, 1243;  
 NMR δ (CDCl<sub>3</sub>): 1.26 (3H, m), 1.35 (3H, d, J = 6.3 Hz), 2.92 (1H, m), 2.30 - 2.85 (7H, m), 3.34  
 (3H x 0.5, s), 3.56 (3H x 0.5, s), 3.20 - 3.83 (9H, m), 4.20 (2H, m), 4.76 (1H, m),  
 5.08 - 5.55 (4H, m), 7.44 (2H x 0.5, d, J = 8.9 Hz), 7.52 (2H x 0.5, d, J = 8.6  
 Hz), 7.65 (2H, d, J = 8.9 Hz), 8.20 (4H, m).

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Reference Example 51

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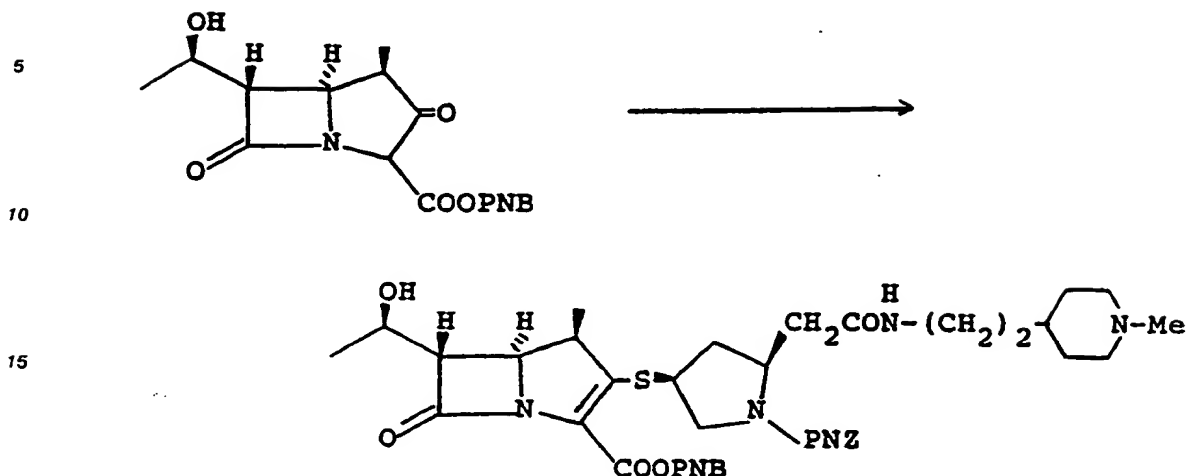
30

To a solution of (4R,5R,6S,8R)-p-nitrobenzyl-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-3,7-  
 dione-2-carboxylate (217 mg) in dry acetonitrile (2.0 ml), diisopropylethylamine (93 mg) and diphenyl  
 chlorophosphate (178 mg) were added under ice-cooling, and the resultant mixture was stirred for 3 hours.  
 A solution of (2S,4S)-p-nitrobenzyloxycarbonyl-2-(2-(1-methylpiperidin-4-yl)ethyl)aminocarbonyl-4-mercap-  
 topyrrolidine (293 mg) and 1,8-diazabicyclo[5.4.0]-7-undecene (218 mg) in a mixture of dry acetonitril (2.0  
 ml) and dry tetrahydrofuran (4.0 ml) was added to the reaction mixture, followed by stirring for 1 hour. The  
 reaction mixture was combined with a phosphate buffer (pH, 7.0) and extracted with dichloromethane 3  
 times. The organic layer was dried over anhydrous magnesium sulfate. After removal of the solvent, the  
 residue was purified by silica gel column chromatography to give (4R,5S,6S,8R,2'S,4'S)-p-nitrobenzyl-3-[1-  
 p-nitrobenzyloxycarbonyl-2-((2-(1-methylpiperidin-4-yl)ethyl)aminocarbonyl)pyrrolidin-4-ylthio]-4-methyl-6-(1-  
 hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-en-7-one-2-carboxylate.

IR<sub>max</sub> cm<sup>-1</sup> (neat): 3300, 1762, 1703, 1519, 1487, 1342, 1204;  
 NMR δ (CDCl<sub>3</sub>): 1.24 (3H, d, J = 7.3 Hz), 1.36 (3H, d, J = 6.3 Hz), 2.35 (3H, br.s).

50

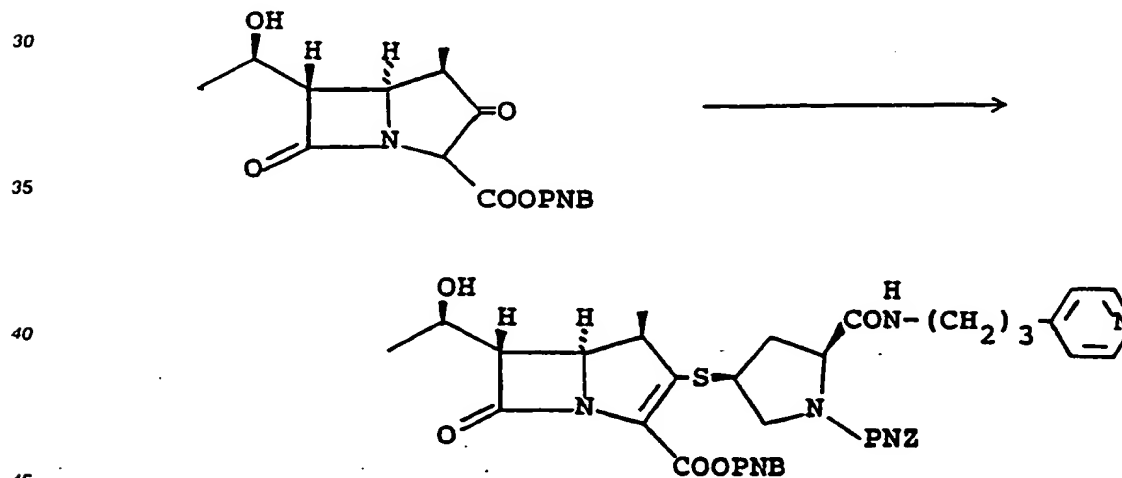
55

Reference Example 52

In the same manner as in Reference Example 51, there was obtained (4R,5S,6S,8R,2'S,4'S)-p-nitrobenzyl-[1-p-nitrobenzyloxycarbonyl-2-((2-(1-methylpiperidin-4-yl)ethyl)aminocarbonylmethyl)pyrrolidin-4-ylthio]-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-en-7-one-2-carboxylate.

IR<sub>max</sub> cm<sup>-1</sup> (neat): 3350, 1758, 1693, 1518, 1339;

25 NMR δ (CDCl<sub>3</sub>): 1.25 (3H, d, J = 7.0 Hz), 1.36 (3H, d, J = 6.3 Hz), 2.35 (3H, br.s).

Reference Example 53

To a solution of (4R,5R,6S,8R)-p-nitrobenzyl-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-3,7-dione-2-carboxylate (256 mg) in dry acetonitrile (1.5 ml), diisopropylethylamine (108 mg) and diphenyl chlorophosphate (206 mg) were added under ice-cooling, and the resultant mixture was stirred at the same temperature for 4 hours. To a suspension of (2S,4S)-1-p-nitrobenzyloxycarbonyl-2-(3-(4-pyridyl)propyl)-aminocarbonyl-4-mercaptopyrrolidine (450 mg) in dry acetonitrile (3.0 ml), bis(trimethylsilyl)acetamide (165 mg) was added, and the mixture was heated to 60 °C, followed by allowing to stand. The thus obtained solution was added to the above phosphate solution under cooling with ice, and diisopropylethylamine (108 mg) was added thereto. After 15 minutes, 1,8-diazabicyclo[5.4.0]-7-undecene (203 mg) was added, followed by stirring for 1 hour. The reaction mixture was diluted with ethyl acetate, washed with aqueous potassium phosphate solution and a saturated aqueous sodium chloride solution in order and dried over anhydrous magnesium sulfate. After removal of the solvent, the residue was dissolved in ethyl acetate (50 ml), 0.1 N hydrochloric acid (5.0 ml) was added while cooling with ice, and the resultant mixture was stirred vigorously.

A phosphate buffer (pH, 7.0) was added to the reaction mixture, which was extracted with dichloromethane three times. The extracts were combined together, dried over anhydrous magnesium sulfate, concentrated and purified by silica gel column chromatography to give (4R,5S,6S,8R,2'S,4'S)-p-nitrobenzyl-3-[1-p-nitrobenzyloxycarbonyl-2-((3-(4-pyridyl)propyl)aminocarbonyl)pyrrolidin-4-ylthio]-4-methyl-6-(1-

5 hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-en-7-one-2-carboxylate.

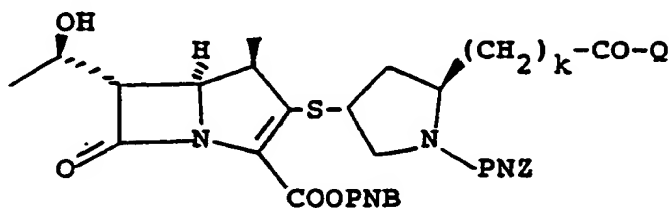
IR<sub>max</sub> cm<sup>-1</sup> (neat): 3350, 1760, 1697, 1518, 1340;

NMR  $\delta$  (CDCl<sub>3</sub>): 1.26 (3H, d, J = 7.0 Hz), 1.36 (3H, d, J = 6.3 Hz), 1.84 (2H, m), 2.60 (2H, m), 7.09 (2H, m), 7.49 (2H, m), 7.62 (2H, m), 8.20 (4H, m), 8.48 (2H, d, J = 5.9 Hz).

#### 10 Reference Examples 54 to 60

In the same manner as in Reference Example 53, the compounds as shown in Table 11 were obtained. The physical properties of the compounds obtained follow the Table.

15 Table 11



	<u>Ref erence Example No.</u>	<u>k</u>	<u>Q</u>
5	54	0	
10	55	0	
15	56	0	
20	57	0	
25	58	0	
30	59	0	
35	60	0	

40

Physical propertiesReference Example 54

45 NMR  $\delta$  (CDCl<sub>3</sub>): 1.26 (3H, d, J = 7.3 Hz), 1.36 (3H, d, J = 6.3 Hz), 5.11 (1H, d, J = 13.5 Hz), 5.18 (2H, m), 5.42 (1H, d, J = 13.5 Hz), 7.00 - 7.80 (6H, m), 8.05 (1H, m), 8.19 (4H, d, J = 8.9 Hz), 8.39 (1H, m).

Reference Example 55

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IR<sub>max</sub> cm<sup>-1</sup> (neat): 3400, 1742, 1680, 1500, 1309, 1251;  
 NMR  $\delta$  (CDCl<sub>3</sub>): 1.27 (3H, d, J = 6.9 Hz), 1.36 (3H, d, J = 6.3 Hz), 1.95 (1H, m), 2.51 (1H, m), 2.84 (2H, m), 3.32 (2H, m), 3.49 (3H, m), 3.73 (1H, m), 3.97 (1H, m), 5.20 (3H, m), 5.42 (1H, d, J = 13.5 Hz), 7.23 (1H, m), 7.51 (3H, m), 7.62 (2H, d, J = 8.6 Hz), 8.18 (4H, d, J = 8.6 Hz), 8.43 (2H, m).

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Reference Example 56

IR<sub>max</sub> cm<sup>-1</sup> (neat): 3225, 1770, 1703, 1655, 1518, 1422, 1399, 1342, 1318, 1273, 1203, 1166, 1137, 1105;

NMR δ (CDCl<sub>3</sub>): 1.24 (3H, d, J = 7.3 Hz), 1.35 (3H, d, J = 6.3 Hz), 1.82 (3H, m), 2.61 (2H, m), 3.36 (4H, m), 3.50 (1H, m), 3.76 (1H, m), 4.08 (1H, m), 4.28 (2H, m), 4.38 (1H, m), 5.14 (1H, d, J = 13.9 Hz), 5.24 (2H, br. s), 5.40 (1H, d, J = 13.9 Hz), 7.20 (1H, t, J = 6.0 Hz), 7.48 (3H, br.s), 7.62 (2H, d, J = 8.6 Hz), 8.18 (4H, d, J = 8.3 Hz), 8.42 (2H, br. s).

#### Reference Example 57

IR<sub>max</sub> cm<sup>-1</sup> (neat): 3400, 1767, 1703, 1647, 1520, 1422, 1403, 1343, 1262;

NMR δ (CDCl<sub>3</sub>): 1.26 (3H, d, J = 7.3 Hz), 1.37 (3H, d, J = 6.0 Hz), 2.16 (1H, m), 2.60 (3H, m), 3.27 (5H, m), 3.47 (1H, m), 3.73 (1H, m), 4.02 (1H, m), 4.32 (3H, m), 5.23 (3H, m), 5.46 (1H, d, J = 13.9 Hz), 7.22 (1H, m), 7.46 (3H, m), 7.64 (2H, d, J = 8.9 Hz), 8.21 (4H, d, J = 8.9 Hz), 8.42 (2H, m).

#### Reference Example 58

NMR δ (CDCl<sub>3</sub>): 1.27 (3H, d, J = 7.3 Hz), 1.36 (3H, d, J = 6.3 Hz), 3.29 (1H, dd, J = 3.0 & 5.9 Hz), 5.17 (1H, d, J = 12.9 Hz), 5.23 (2H, br.s), 5.42 (1H, d, J = 12.9 Hz), 7.18 (2H, m), 7.48 (2H, m), 7.63 (2H, d, J = 8.9 Hz), 8.22 (4H, m), 8.51 (2H, m).

#### Reference Example 59

IR<sub>max</sub> cm<sup>-1</sup> (neat): 3370, 1756, 1682, 1597, 1510, 1420, 1392, 1335, 1196, 1103;

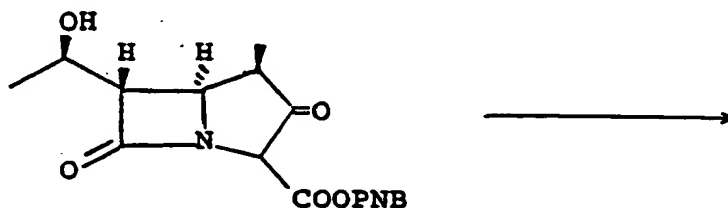
NMR δ (CDCl<sub>3</sub>): 1.27 (3H, d, J = 7.3 Hz), 1.34 (3H, d, J = 6.3 Hz), 2.49 (3H, s), 2.78 (2H, m), 3.29 (1H, dd, J = 2.3 & 6.6 Hz), 3.34 (1H, m), 3.49 (2H, m), 3.74 (1H, m), 4.00 (1H, m), 4.27 (2H, m), 4.36 (1H, m), 5.17 (1H, d, J = 13.9 Hz), 5.19 (2H, s), 5.42 (1H, d, J = 13.9 Hz), 7.07 (1H, d, J = 7.9 Hz), 7.44 (3H, m), 7.60 (2H, d, J = 8.9 Hz), 8.16 (4H, d, J = 8.9 Hz), 8.28 (1H, s).

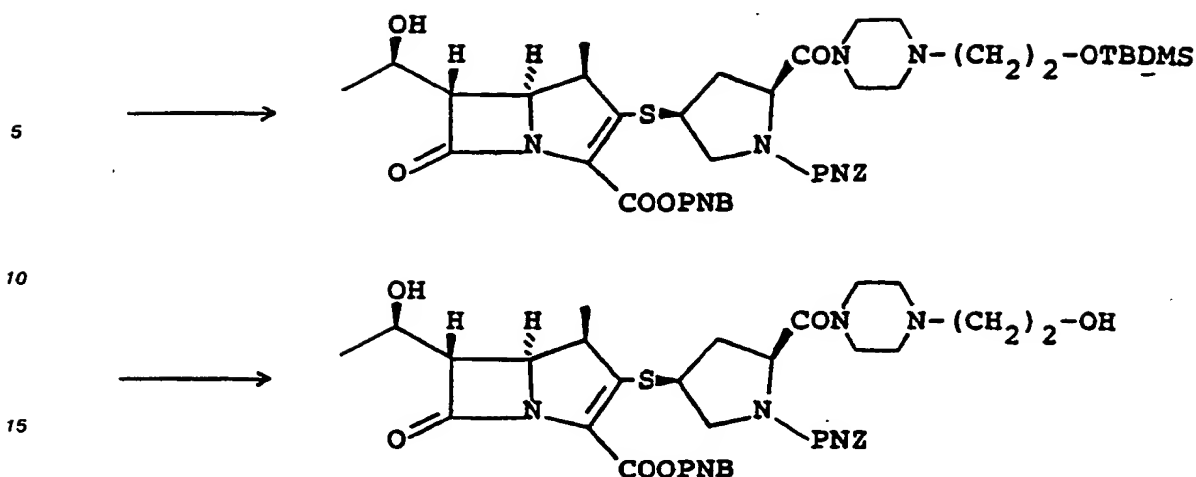
#### Reference Example 60

IR<sub>max</sub> cm<sup>-1</sup> (neat): 3400, 1767, 1703, 1521, 1441, 1399, 1343, 1262, 1203;

NMR δ (CDCl<sub>3</sub>): 1.24 (3H, d, J = 7.3 Hz), 1.37 (3H, d, J = 6.3 Hz), 2.56 (3H, s), 2.84 (2H, m), 3.20 - 3.65 (6H, m), 3.73 (1H, m), 4.08 (1H, m), 4.20 - 4.45 (4H, m), 5.20 (1H, d, J = 13.5 Hz), 5.19 (2H, br. s), 5.45 (1H, d, J = 13.5 Hz), 7.04 (1H, dd, J = 4.9 & 7.6 Hz), 7.43 (1H, d, J = 7.6 Hz), 7.50 (2H, m), 7.63 (2H, d, J = 8.6 Hz), 8.21 (4H, d, J = 8.6 Hz), 8.35 (1H, d, J = 4.9 Hz).

#### Reference Example 61





20 a) To a solution of (4R,5R,6S,8R)-p-nitrobenzyl-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-3,7-dione-2-carboxylate (256 mg) in dry acetonitrile (2.0 ml), diisopropylethylamine (108 mg) and diphenyl chlorophosphate (200 mg) were added under ice-cooling, and the resultant mixture was stirred at the same temperature for 2 hours. A solution of 1-p-nitrobenzyloxycarbonyl-2-(4-(2-(t-butyldimethylsilyloxy)ethyl)piperazin-2-ylcarbonyl)-4-mercaptopyrrolidine (491 mg) and diisopropylethylamine (108 mg) in dry acetonitrile (2.0 ml) was added thereto, followed by stirring for 2 hours. The reaction mixture was diluted with ethyl acetate, washed with aqueous potassium phosphate solution and a saturated aqueous sodium chloride solution in order and dried over anhydrous magnesium sulfate. After removal of the solvent, the residue was purified by silica gel column chromatography to give (4R,5S,6S,8R,2'S,4'S)-p-nitrobenzyl-3-[1-p-nitrobenzyloxycarbonyl-2-(4-(2-(t-butyldimethylsilyloxy)ethyl)piperazin-1-ylcarbonyl)pyrrolidin-4-ylthio]-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-en-7-one-2-carboxylate.

30 IR<sub>max</sub> cm<sup>-1</sup> (neat): 3250, 1763, 1703, 1664, 1657, 1521, 1342;  
NMR δ (CDCl<sub>3</sub>): 0.06 (6H, s), 0.89 (9H, s), 1.29 (3H, d, J = 7.3 Hz), 1.37 (3H, d, J = 6.3 Hz), 2.50 (6H, m), 3.38 (2H, m), 3.56 (2H, m), 3.76 (2H, m), 5.10 - 5.55 (4H, m), 7.40 - 7.60 (2H, m), 7.65 (2H, d, J = 8.3 Hz), 8.24 (4H, m).

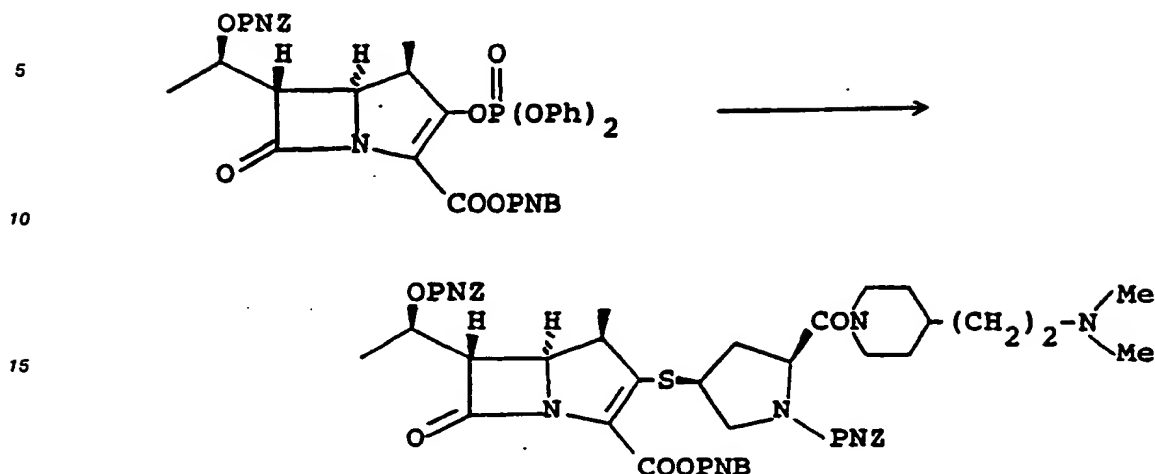
35 b) The thus obtained (4R,5S,6S,8R,2'S,4'S)-p-nitrobenzyl-3-[1-p-nitrobenzyloxycarbonyl-2-(4-(2-(t-butyldimethylsilyloxy)ethyl)piperazin-1-ylcarbonyl)pyrrolidin-4-ylthio]-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-en-7-one-2-carboxylate (476 mg) was dissolved in dry tetrahydrofuran (4.0 ml) and stirred at room temperature. Acetic acid (657 mg) and a 1 N tetrahydrofuran solution of tetrabutylammonium fluoride (2.16 ml) were added, and the resultant mixture was stirred at the same temperature for 9 hour. A phosphate buffer (pH, 7.0) was added to the reaction mixture, which was extracted with dichloromethane three times. The organic layer was dried over anhydrous magnesium sulfate, followed by removal of the solvent. The residue was purified by silica gel column chromatography to give (4R,5S,6S,8R,2'S,4'S)-p-nitrobenzyl-3-[1-p-nitrobenzyloxycarbonyl-2-(4-(2-hydroxyethyl)piperazin-1-ylcarbonyl)pyrrolidin-4-ylthio]-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-en-7-one-2-carboxylate.

45 IR<sub>max</sub> cm<sup>-1</sup> (neat): 3250, 1762, 1703, 1658, 1521, 1342;  
NMR δ (CDCl<sub>3</sub>): 1.28 (3H, d, J = 7.3 Hz), 1.36 (3H, d, J = 6.0 Hz), 1.92 (1H, m), 2.80 (6H, m), 2.93 (1H, m), 3.20 - 3.80 (9H, m), 4.08 (1H, m), 4.26 (3H, m), 4.73 (1H, m), 5.25 (3H, m), 5.49 (1H, d, J = 13.8 Hz), 7.35 - 7.60 (2H, m), 7.64 (2H, d, J = 8.9 Hz), 8.22 (4H, m).

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## Reference Example 62



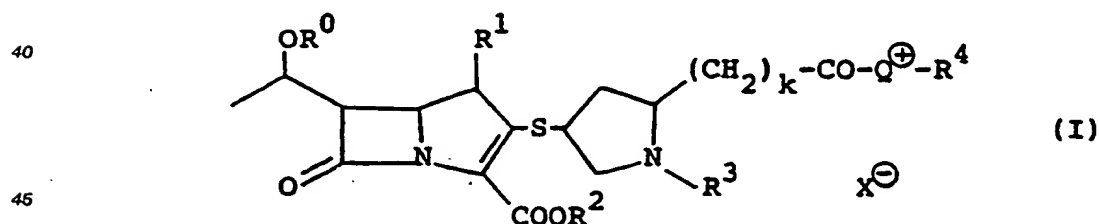
To a solution of (4R,5R,6S,8R)-p-nitrobenzyl-3-(diphenylphosphoryloxy)-4-methyl-6-(1-(p-nitrobenzyloxycarbonyloxy)ethyl)-1-azabicyclo[3.2.0]hept-2-en-7-one-2-carboxylate (714 mg) in dry acetonitrile (3.0 ml), a solution of (2S,4S)-1-p-nitrobenzyloxycarbonyl-2-(4-(2-dimethylaminoethyl)piperidin-1-ylcarbonyl)-4-mercaptopyrrolidine (505 mg) in dry acetonitrile (3.0 ml) was added under ice-cooling, and 1,8-diazabicyclo[5.4.0]-7-undecene (182 mg) was added thereto, followed by stirring at the same temperature for 2 hours. The reaction mixture was diluted with dichloromethane, washed with a saturated aqueous sodium chloride solution and dried over anhydrous magnesium sulfate. After removal of the solvent, the residue was purified by silica gel column chromatography to give (4R,5S,6S,8R,2'S,4'S)-p-nitrobenzyloxycarbonyl-3-[1-p-nitrobenzyl-2-(4-(2-dimethylaminoethyl)piperidin-1-ylcarbonyl)pyrrolidin-4-ylthio]-4-methyl-6-(1-(p-nitrobenzyloxycarbonyloxy)ethyl)-1-azabicyclo[3.2.0]hept-2-en-7-one-2-carboxylate.

NMR  $\delta$  (CDCl<sub>3</sub>): 1.22 (3H, d, J = 7.3 Hz), 1.29 (3H, d, J = 6.3 Hz), 2.38 (6H, s), 5.00 - 5.50 (6H, m), 7.00 - 7.70 (6H, m), 8.18 (6H, m).

## Claims

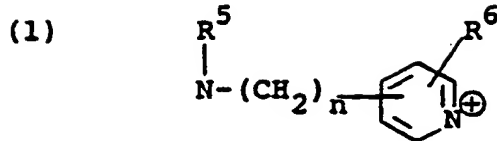
35

1. A compound of the formula:

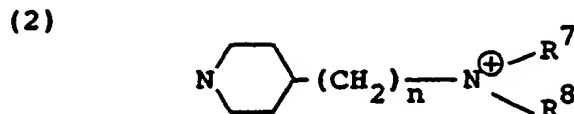


wherein R<sup>0</sup> is a hydrogen atom or a protective group for hydroxyl, R<sup>1</sup> is a lower alkyl group, R<sup>2</sup> is a protective group for carboxyl or a negative charge, R<sup>3</sup> is a hydrogen atom or a protective group for amino, R<sup>4</sup> is a lower alkyl group or a substituted lower alkyl group, k is an integer of 0 to 4, X is an acid residue or an intramolecular COO when R<sup>2</sup> is the negative charge and Q<sup>+</sup> is a quaternary nitrogen atom-containing group represented by either one of the formulas (1) to (4):

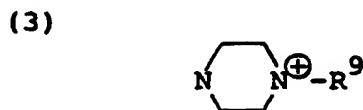
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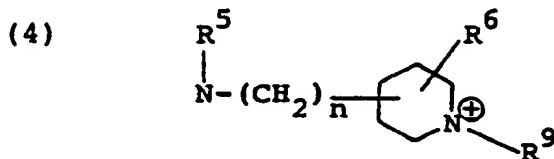
wherein  $R^5$  is a hydrogen atom, a lower alkyl group or a 2-hydroxyethyl group,  $R^6$  is a hydrogen atom or a lower alkyl group and  $n$  is an integer of 0 to 4;



wherein  $R^7$  and  $R^8$  are each a lower alkyl group or may be combined together to form a lower alkylene group, or  $R^8$  represents a substituted lower alkyl group and  $n$  is as defined above;



wherein  $R^9$  is a lower alkyl group or a substituted lower alkyl group; or



wherein  $R^5$ ,  $R^6$ ,  $R^9$  and  $n$  are each as defined above, or its salt.

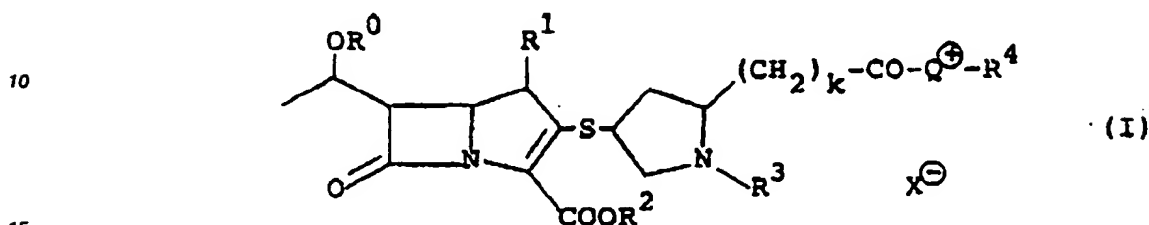
2. The compound according to claim 1, wherein  $R^0$  and  $R^3$  are each a hydrogen atom,  $R^2$  is a negative charge and  $X$  is an intramolecular COO, or its salt.
3. The compound according to claim 2, wherein  $Q^*$  is a quaternary nitrogen atom-containing group represented by either one of the formulas (1) and (3).
4. The compound according to claim 3, wherein  $Q^*$  is a quaternary nitrogen atom-containing group represented by the formula (1) wherein  $R^5$  is a hydrogen atom or a methyl group,  $R^6$  is a hydrogen atom and  $n$  is an integer of 0 to 4.
5. The compound according to claim 3, wherein  $Q^*$  is a quaternary nitrogen atom-containing group represented by the formula (3) wherein  $R^9$  is a methyl group.
6. The compound according to claim 1, wherein  $R^4$  is a  $C_1$ - $C_5$  alkyl group, a  $C_2$ - $C_5$  alkanoyl( $C_1$ - $C_5$ )alkyl group, a carbamoyl( $C_1$ - $C_5$ )alkyl group, a  $C_1$ - $C_5$  alkylaminocarbonyl( $C_1$ - $C_5$ )alkyl group, a di( $C_1$ - $C_5$ )-alkylaminocarbonyl( $C_1$ - $C_5$ )alkyl group or a hydroxy( $C_2$ - $C_5$ )alkyl group.
7. The compound according to claim 1, wherein  $R^1$  is a methyl group.
8. The compound according to claim 1, wherein  $k$  is zero.



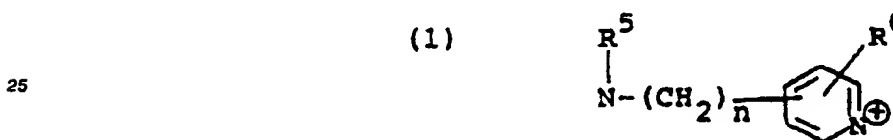
9. The compound according to claim 1, which has a (5S)-configuration.

10. The compound according to claim 1, which has a (4R,5S,6S,8R)-configuration.

11. A process for producing a compound of the formula:



wherein  $R^0$  is a hydrogen atom or a protective group for hydroxyl,  $R^1$  is a lower alkyl group,  $R^2$  is a protective group for carboxyl or a negative charge,  $R^3$  is a hydrogen atom or a protective group for amino,  $R^4$  is a lower alkyl group or a substituted lower alkyl group,  $k$  is an integer of 0 to 4,  $X$  is an acid residue or an intramolecular COO when  $R^2$  is the negative charge and  $Q^+$  is a quaternary nitrogen atom-containing group represented by either one of the formulas (1) to (4):



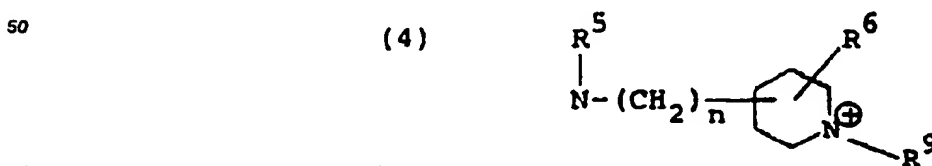
wherein  $R^5$  is a hydrogen atom, a lower alkyl group or a 2-hydroxyethyl group,  $R^6$  is a hydrogen atom or a lower alkyl group and  $n$  is an integer of 0 to 4;



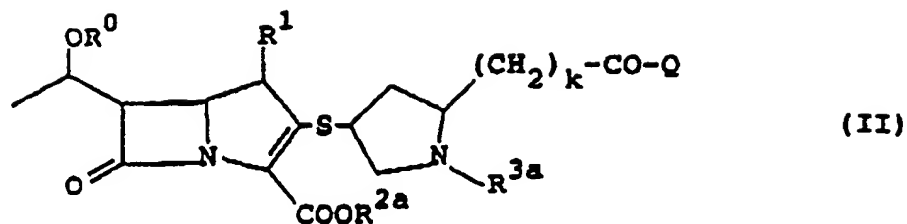
wherein  $R^7$  and  $R^8$  are each a lower alkyl group or may be combined together to form a lower alkylene group, or  $R^8$  represents a substituted lower alkyl group and  $n$  is as defined above;



wherein  $R^9$  is a lower alkyl group or a substituted lower alkyl group; or



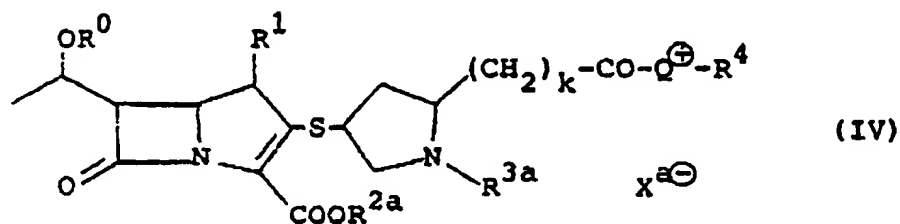
wherein  $R^5$ ,  $R^6$ ,  $R^9$  and  $n$  are each as defined above, or its salt, which comprises reacting a compound of the formula:



10 wherein  $R^0$ ,  $R^1$  and  $k$  are each as defined above,  $R^{2a}$  is a protective group for carboxyl,  $R^{3a}$  is a protective group for amino and  $Q$  is a tertiary nitrogen atom-containing group resulting from elimination of a positive charge from either one of the groups (1) to (4) represented by  $Q^+$  with a compound of the formula:



wherein  $R^4$  is as defined above and  $X^a$  is an acid residue to give a compound of the formula:



25 wherein  $R^0$ ,  $R^1$ ,  $R^{2a}$ ,  $R^{3a}$ ,  $R^4$ ,  $k$ ,  $Q^+$  and  $X^a$  are each as defined above, optionally followed by subjecting the latter to reaction for elimination of the hydroxyl-protecting group represented by  $R^0$ , the carboxyl-protecting group represented by  $R^{2a}$  and/or the amino-protecting group represented by  $R^{3a}$ , thereby giving the compound (I) wherein  $R^0$  and  $R^3$  are each a hydrogen atom and  $R^2$  is a negative charge.

30 12. A pharmaceutical composition which comprises as an active ingredient a pharmaceutically effective amount of at least one of the compounds as claimed in any preceding claim, and at least one pharmaceutically acceptable inert carrier or diluent.

35 13. Use of a compound according to claim 1 as an antimicrobial agent.



European  
Patent Office

## EUROPEAN SEARCH REPORT

Application Number

EP 91 10 2101

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.8)
Y	EP-A-0 243 686 (SUMITOMO) " Claims "	1,7-13	C 07 D 477/00 A 61 K 31/40
Y	EP-A-0 182 213 (SUMITOMO) " Claims "	1,7-13	
A	EP-A-0 126 587 (SUMITOMO) " Claims "	1,7-13	
A	EP-A-0 242 134 (MERCK) " Claims "	1,12,13	
			TECHNICAL FIELDS SEARCHED (Int. Cl.8)
			C 07 D 477/00 A 61 K 31/00
The present search report has been drawn up for all claims			
Place of search The Hague		Date of completion of search 18 April 91	Examiner CHOULY J.
<div>CATEGORY F CITED DOCUMENTS</div> <div>E: earlier patent document, but published on, or after the filing date</div> <div>D: document cited in the application</div> <div>L: document cited for other reasons</div> <div>A: technological background</div> <div>O: non-written disclosure</div> <div>P: intermediate document</div> <div>T: theory or principle underlying the invention</div> <div>&amp;: member of the same patent family, corresponding document</div>			